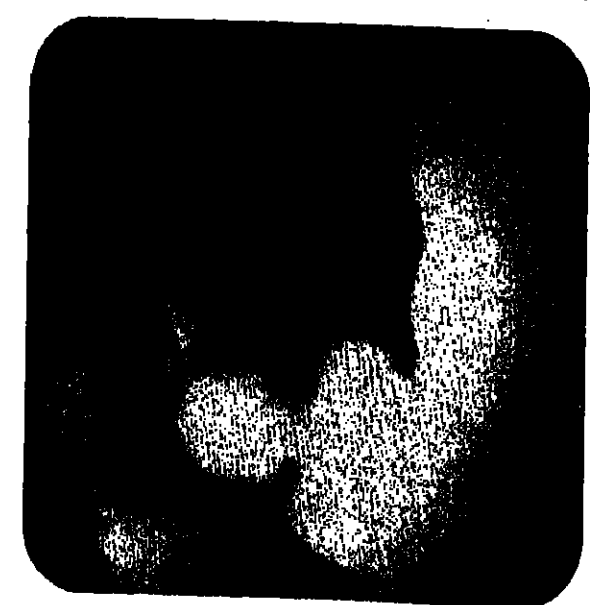


The Upper Functional G.I. Disorder

# The Pseudo-ulcer



Ulcer-like symptoms: no G.I. pathology

The patient is convinced it's an ulcer. However, symptoms are not quite typical, and x-ray findings are negative. These findings and the results of additional diagnostic procedures exclude an organic basis for the patient's complaints. A diagnosis of "upper functional gastrointestinal disorder" is made, which is supported by the fact that episodes of painful symptoms coincide with episodes of excessive anxiety, as indicated by the history.

It may be useful to explain to the patient the mechanism by which emotions upset normal G.I. functioning, resulting in hypersecretion and hypermotility and thus causing such symptoms as nausea and epigastric pain. In upper functional gastrointestinal disorders, counseling by the primary physician can often help the patient to understand how excessive anxiety may cause flare-ups of G.I. symptoms.

A disproportionate number of patients seen by the general practitioner suffer from functional disorders, as do more than half of those seen by the gastroenterologist. \* Where milder cases may respond to counsel-

ing alone, if symptoms are severe and disabling to any degree, a suitable regimen may include medication to reduce the symptoms and the excessive anxiety that often provokes these distressing symptoms. In these cases, Librax as an adjunct can greatly contribute to the course of therapy. Its dual action can offer relief of both painful symptoms and excessive anxiety, because each capsule contains 5 mg chlorthalidone HCl and 2.5 mg clidinium Br. The antianxiety action of Librium® (chlordiazepoxide HCl) makes Librax exceptional

An adjunct in anxiety-related upper functional G.I. disorders

## Librax®

Each capsule contains 5 mg chlorthalidone HCl and 2.5 mg clidinium Br.

Before prescribing, please consult complete product information, a summary of which follows:

**Indications:** Symptomatic relief of hypersecretion, hypermotility and anxiety and tension states associated with organic or functional gastrointestinal disorders; and as adjunctive therapy in the management of peptic ulcer, gastritis, duodenitis, irritable bowel syndrome, spastic colitis, and mild ulcerative colitis.

**Contraindications:** Patients with glaucoma; prostatic hypertrophy and benign bladder neck obstruction; known hypersensitivity to chlorthalidone hydrochloride and/or clidinium bromide.

**Warnings:** Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering Librium (chlordiazepoxide hydrochloride) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions, following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in

pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards. As with all anticholinergic drugs, an inhibiting effect on lactation may occur.

**Precautions:** In elderly and debilitated, limit dosage to smallest effective amount to preclude development of ataxia, oversedation or confusion (not more than two capsules per day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentially interacting drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

**Adverse Reactions:** No side effects or manifestations not seen with either compound alone have been reported with Librax. When chlorthalidone hydrochloride is used alone, drowsi-

ness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally with chlorthalidone hydrochloride, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax are typical of anticholinergic agents, i.e., dryness of mouth, blurring of vision, urinary hesitancy and constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

**ROCHE** Roche Laboratories Division of Hoffmann-La Roche Inc. Nutley, New Jersey 07110

Med Trib 13

# Medical Tribune

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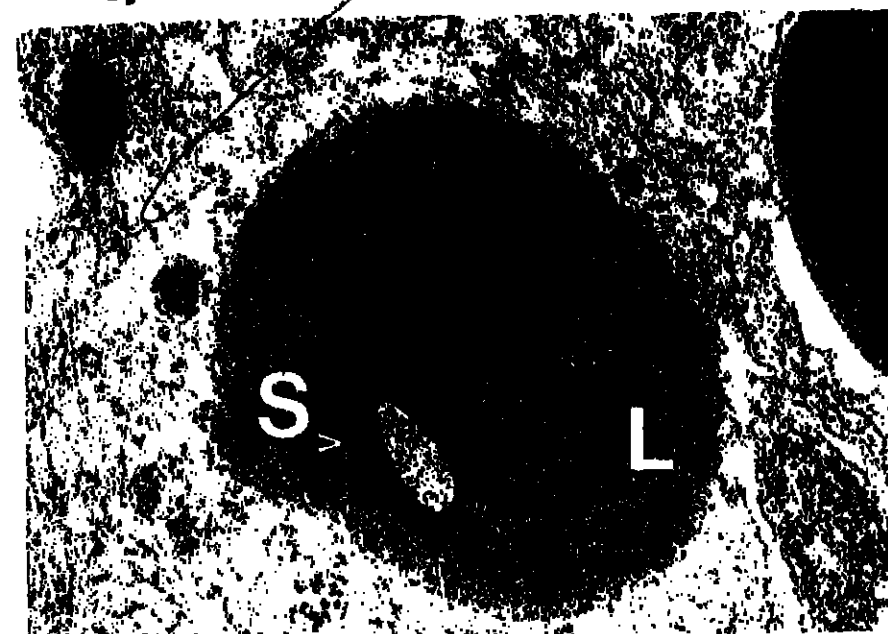
Vol. 16, No. 13

world news of medicine and its practice—fast, accurate, complete

and Medical News

Wednesday, April 2, 1975

## Lysosome 'Tricked' Into Accepting Enzyme



Liposome "spansule" (S) carrying peroxidase and coated with immunoglobulin is shown having fused with dogfish lysosomes (L) within phagocyte in these electron micrographs. Similar method of supplying enzymes to deficient human lysosomes may have application in Tay-Sachs and other degenerative diseases of C.N.S.

## Biological Engineering Is Used To Put Enzymes in Lysosomes

By EDWARD GROSSMAN  
Medical Tribune Staff

NEW YORK—Using phagocytes of the dogfish shark, Dr. Gerald Weissmann of the New York University Medical Center and a group of his students have devised a method of "tricking" lysosomes into taking up missing enzymes. The method, which depends on spansule-like artificial "liposomes" to deliver the enzymes into the lysosomes, may have clinical application in the treatment of a number of sphingolipidoses enzyme-deficiency diseases, including Tay-Sachs Disease, Dr. Weissmann indicated.

Dr. Weissmann told MEDICAL TRIBUNE that preliminary data from in vitro

studies of tissue from three Tay-Sachs patients shows "some promise" that the new method could be useful in delivering enzymes efficiently in humans.

The dogfish shark was chosen for an experimental model because it lacks peroxidase, a lysosomal enzyme similar to those which are absent in patients with Tay-Sachs and related disorders. In humans the lack of these enzymes leads to intracellular build-up of unmetabolized lipids in the central nervous system, progressive degeneration, and death.

Dr. Weissmann's group utilized dogfish phagocytes to take up peroxidase enzyme, which had been captured by

Continued on page 3

## Antiabortion Shift Worries Europe MDs

By JAMES MAGEE  
Medical Tribune World Service

GENEVA—Signs of a conservative political backlash on abortion have left many physicians in Switzerland, West Germany, and Italy wondering whether they are facing prosecution.

In West Germany, legislation that would have brought that country into line with France and the United Kingdom—permitting abortion virtually without restriction during the first trimester—has been blocked by the constitutional court after having been accepted in parliament by a large majority.

Given the scale of abortions in Germany—one estimate puts the total at between 800,000 and 1,200,000 a year—the decision has not only created fresh public controversy but has also caused apprehension and bewilderment among physicians.

In Switzerland, where three projects are under study for a change in the abortion laws, the medical profession is also feeling increasingly exposed.

This has been underlined by the decision by one cantonal court to hand down suspended prison sentences and assess heavy fines against three physicians who have been regularly carrying out abortions.

Continued on page 19

## When to Do T&A? 30 Surveys Fail To Resolve Issue

Medical Tribune World Service

WINNIPEG, MAN.—T&As—should they or shouldn't they be done and when? A team of physicians at McMaster University in Hamilton, Ont., reviewed 30 surveys of tonsillectomies, and concluded that all of the surveys were lacking in one respect or another.

If the question is to be resolved, they told the Royal College of Physicians and Surgeons of Canada here, what's needed is another survey.

The question should be resolved, they said, because T&As are both costly and risky. In Canada in 1971, there were 161,301 of the procedures performed at a cost of \$25,600,000 with a mortality rate of approximately one death in 10,000 procedures. Dr. William Feldman who headed the survey team, proposed "a prospective, randomized, controlled clinical trial quantifying outcome by objective tech-

Continued on page 13

## Noninvasive Technique



Average frequency spectrum of 8 systolic bruits in patient with stenosis of residual diameter 2.0 mm. Cross hairs mark "break frequency," at which intensity falls off sharply; frequency was found inversely related to diameter of stenotic segment.

## Phonoangiography Indicates Degree Of Carotid Stenosis

By FRANCES GOODNIGHT  
Medical Tribune Staff

HOUSTON—Successful use of noninvasive phonoangiography to predict the degree of carotid artery stenosis in patients with atherosclerotic vascular disease has been achieved by a team of investigators at Massachusetts General Hospital and the Massachusetts Institute of Technology.

A clinical trial of the new technique in 48 patients having carotid bruits yielded results that "compared favorably" with those obtained by a standard carotid arteriogram, the American College of Cardiology was told here.

Describing the procedure, M.I.T. graduate student James O. Gruber said that phonoangiography provides quantitative information about the relationship between the diameter of a narrowed artery and the frequency-intensity spectrum of the sound produced by turbulent flow at the stenosis.

Data are gathered by placing a pressure-sensitive microphone on the skin over the artery. Bruits are recorded with a tape recorder, the taped signal is transmitted to a minicomputer via an analog-digital converter, and the digitized signal is then displayed on a cathode ray tube.

Dr. Robert S. Lees, one of the research group's senior investigators and director of the M.G.H. Non-Invasive Diagnostic Laboratory, commented during a news conference that he believes phonoangiography will become a useful screening procedure because of its comparative simplicity, its noninvasive nature, and the fact that it can be done on an outpatient basis.

Although Dr. Lees does not expect the new technique to replace arteriography, he foresees that it will serve to

Continued on page 13

making rounds at press time

INTERN & RESIDENT STRIKE in N.Y. City should have "broad range implications for house staff across the country if substantial gains are achieved in the areas of more reasonable hours and elimination of out-of-title work," the president of the Physicians National Housestaff Association, Dr. Robert Barrow, said.

TOUGHER LICENSING LAWS are being sought by Washington D.C. Medical Society, according to its president, Dr. William Cooper. "Right now, the law says a physician's license can't be touched unless he's convicted and sentenced for a felony. In most other states, medical licenses can be suspended or revoked for professional misconduct," executive director Francis Ferraraccio told MT. The society proposes expanding local licensing commission to include a majority of M.D.s.

## Exclusive Medical Tribune Report—IV

## Assessing Adverse Drug Reactions

This is the fourth article in a series presenting highlights from an objective study of adverse drug reactions sponsored by Medicine in the Public Interest. The study was made by two leading pharmacologists, Drs. Fred Karch and Louis Lasagna of the University of Rochester School of Medicine and Dentistry.

The true dimensions of the adverse reaction (ADR) problem was one of the primary interests of the Karch and Lasagna report for Medicine in the Public Interest, a nonprofit organization that carries out research related to health and evaluations "that the government cannot or will not perform" objectively. Witnesses before the Senate subcommittee on health had extrapolated data from a few limited studies to project as many as 140,000 deaths per year from ADRs.

After reviewing this data, Drs. Karch and Lasagna concluded that these estimates "are completely unreliable" because their data base was "incomplete, unrepresentative, uncontrolled and not operationally identified." They pointed out that "no statistically valid estimates can be derived from such data."

Nevertheless they did not dismiss the problem. "One can scarcely think of a more critical issue," they said. "It is one thing if a patient, without a prior history of allergy, develops a severe re-

The full MIPI report on adverse drug reactions can be obtained at \$1.50 a copy from Medicine in the Public Interest, Suite 720, 600 New Hampshire Ave., N.W., Washington, D.C. 20037.

assessments, such as "definite," "probable," "possible," "conditional" and "doubtful," as was done by the Registry of Tissue Reactions to Drugs.

"Evaluation of adverse drug reactions based on 'definite' or 'probable' reactions should eliminate many 'false-positive' reactions—that is, reactions which might be interpreted as adverse drug reactions, but in fact are not."

## Fourth of a Series

## Need for Research

action to an antibiotic, appropriately chosen and prescribed in proper dosage for the proper length of time, in the treatment of lobar pneumonia, and quite another if the same event occurs in someone given the same antibiotic in the same way to treat viral hepatitis. The first represents an unfortunate but necessary risk that must be run, because failure to treat involves worse risks; the second is a totally unjustified risk taken without anticipation of benefit.

## Moratorium: "Reckless Statements"

Yet the magnitude of the problem cannot be presently ascertained from available data. This led Drs. Karch and Lasagna to assert "a moratorium on reckless statements and estimates" as well as "more complete data" were "desperately needed."

In the MIPI study Drs. Karch and Lasagna pointed out that one of the deficiencies of many studies was a poor defining of what a drug was, what an adverse drug reaction was, and a general lack of perspective on the problem. "Our survey strongly suggests that alcohol is responsible for more hospitalizations than all the ethical drugs put together," they said in calling for perspective and definitions.

Characterizing a drug as "a chemical substance or product available for an intended diagnostic, prophylactic, or therapeutic purpose for the benefit of the recipient," Drs. Karch and Lasagna defined an adverse drug reaction as "any response to a drug which is noxious and unintended and which occurs at dosages used in man for prophylaxis, diagnosis or therapy, excluding therapeutic failures."

Because one of the major difficulties in "discerning whether a particular event in a given patient is the result of a specific medication or is simply part of the patient's underlying illness," they urged close attention be paid to this complex linkage. They called for establishment of definite standardized as-

sessments, such as "definite," "probable," "possible," "conditional" and "doubtful," as was done by the Registry of Tissue Reactions to Drugs.

"Evaluation of adverse drug reactions based on 'definite' or 'probable' reactions should eliminate many 'false-positive' reactions—that is, reactions which might be interpreted as adverse drug reactions, but in fact are not."

At present the marketing of drugs is subject to special national authorization procedures which vary considerably from one E.E.C. country to another. In addition, a product which crosses a frontier is often again subjected to time-consuming checks to test the drug's degree of toxicity, its therapeutic effects and conformity with its stated formula.

Over the next 18 months, however,

Dr. Weissmann

This is the first successful introduction of enzymes by biological engineer-

## Vitreotomy With New Instrument in Seattle



With its new Vitreous Infusion Suction Cutter, the University of Washington Hospital, Seattle, has become the Pacific Northwest's major referral center for vitrectomies. During the procedure, the surgeon makes a small incision in the eye and, using an operating microscope, introduces the instrument into the opaque vitreous, above. The vitreous is then cut and is removed by suction. A saline solution is simultaneously infused to replace it. Eventually, the saline is supplanted by normal eye fluids.

ago an international conference on ADRs was held in Washington. "The conferees agreed on the need for a national approach to drug surveillance. It is unfortunate that we are no closer to a concerted effort to define both the good and the bad effects of drugs, so that their optimal place in our society can be defined," they concluded.

Next week Medical Tribune will present an article by Dr. Dana L. Farnsworth, of the Harvard University School of Public Health and chairman of the Board of Trustees of Medicine in the Public Interest, summarizing current medical opinion with regard to adverse drug reactions following the MIPI report on the problem.

## EEC Expedites Movement of Drug Products

By JAMES MAGEE  
Medical Tribune World Service

BRUSSELS—A lot of the red tape that up to now has bedeviled the movement of pharmaceutical products across borders in the European Economic Community has been removed by directives approved here by the E.E.C. council of ministers.

The directives, which come on the heels of the agreement to allow free movement of doctors in the nine E.E.C. member-countries, will help to reduce prices by lowering administrative costs and rationalizing production.

At present the marketing of drugs is subject to special national authorization procedures which vary considerably from one E.E.C. country to another. In addition, a product which crosses a frontier is often again subjected to time-consuming checks to test the drug's degree of toxicity, its therapeutic effects and conformity with its stated formula.

Over the next 18 months, however,

Dr. Weissmann

This is the first successful introduction of enzymes by biological engineer-

member-states must take steps to conform to standard criteria for national authorization, including labeling requirements and quality controls. Once a product has been authorized in one E.E.C. country it will no longer be subject to checks in a second country.

The authorization requirements are searching. A manufacturer who wants clearance must show that he has adequate premises and equipment, the necessary staff to test both the raw materials and finished product, and provide detailed information of the results.

Furthermore, the package leaflet will also have to show all the constituents of the product, the method of preparation, full therapeutic indications, contraindications and side-effects, dosage, method of administration, and storage advice. The leaflet must also indicate the trademark, distributor's or manufacturer's name and address, and the expiration date if shelf-life is less than three years.

The authorization must be refused,

Dr. Weissmann

This is the first successful introduction of enzymes by biological engineer-

or revoked, if the product proves harmful, does not conform to the stated therapeutic effects, or does not match the manufacturer's declared specifications.

The new rules also include a decision to set up a special E.E.C. committee, consisting of health officials of the nine countries, which will not only supervise the authorization system but also provide a channel for companies who want to seek an authorization valid in several countries at the same time. This will be granted if the product has already been cleared by one E.E.C. country, and the request covers at least five member states.

Pharmaceutical products already in circulation will gradually be brought into the provisions of the new regulations. The rules will not apply, however, to biological products, e.g. vaccines, toxins and serums, human blood products, pharmaceuticals based on radio isotopes, or to homeopathic products.

## Hastings Favors Deliberation On Malpractice Legislation

By ALAN FITZGIBBON  
Special Tribune Correspondent

WASHINGTON—There are no simple solutions to the medical malpractice insurance crisis and any attempt to enact quick remedial legislation might only compound the problem, one of Congress's leading students of medical liability has warned.

"All too often before I've seen the Congress quickly try to respond to a crisis, and we don't really come up with the answers," said Rep. James F. Hastings, who has been examining the problem intensively since early last fall and readily concedes that he wants to study it further before proposing any solutions.

Mr. Hastings, an influential Republican member of the House Subcommittee on Health and Environment from New York, sponsored a national conference on medical malpractice here with the American Group Practice Association.

One of the shortcomings the congressman sees in any emergency corrective measures, such as a no-fault bill which Sen. Daniel K. Inouye (D-Hawaii) introduced in mid-January, is that they deal unequally with the many elements of a complex situation and thus neglect the interests of influential constituencies whose resulting opposition might be strong enough to kill a bill.

Mr. Hastings found two faults with the no-fault approach which he thought unlikely to gain inclusion in any measure that may be passed this year.

First, he said, "I'd have a great concern about saying to the profession of medicine, 'Well, you don't have to be

concerned any more as to the quality of medicine since there's automatic coverage.'"

And, he continued, "The contingency fee [which no-fault insurance would negate] is and has been historically within the states' jurisdiction. I don't know of any precedents for the federal government, and certainly the Congress, getting into that kind of issue. There has been a question raised as to the constitutionality of the federal government involving itself in an across-the-board limitation on the contingency fee system."

"So I just think it's going to take a while to come up with reasonable answers to this problem. We can't afford to take the amount of time it would require to fight the American Bar Association and other legal groups on the constitutionality of lawyers' rights to charge contingency fees."

Asked why he thought the malpractice insurance problem had suddenly reached crisis proportions in the last two months, even though coverage rates for both physicians and hospitals had clearly been increasing in recent years, Mr. Hastings responded:

## Companies' Moves Cited

"Apparently the insurance companies had never made the moves they made earlier this year in New York State, for example, where coverage itself was actually threatened. I suppose that since this had been primarily a state matter, not enough attention had been paid to it. HEW spent 16 months accumulating information for its report on the problem, but apparently they didn't think it was that serious a problem or if they did, they were taking no steps at all to try to suggest some kind of answers. Nor did I hear from the [medical] profession until this year that this represented a crisis for them."

Continued on page 19

## Prader-Willi Treatment



A method of treating children with Prader-Willi syndrome, characterized by mental retardation and by compulsive eating, has been developed by scientists at the University of Washington, Seattle. The before-and-after photos, above and below, show the degree of their success in preventing compulsive eating and stimulating mental development. The emphasis is placed on parental motivation and special classroom work. Of the two failures in the program, one was attributed to failure to enlist the mother's cooperation and the other to severe emotional problems due to the death of the father.



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CLINICAL NEWS NOTE: "... all evaluations of the T&A procedure in the English language literature have methodologic defects in study design, sample, description of illness, treatment, and follow-up which preclude the decision on the validity of these procedures." (Dr. William Feldman, see page 1.)

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... brief summaries of editorials or comments in current medical and scientific journals.

### New Kind of Leper?

"Persons in medicine, dentistry, and allied professions have an enormous stake in their continued ability to give direct health care. . . . Nonetheless, there is the possibility that an estimated 1 per cent or more of health-care professionals, the carriers of hepatitis B virus (HBV), could be barred from contact with patients. A few are already being treated as if they were a new kind of leper.

"The discovery in 1968 that 'Australia' antigen is a serologic marker of HBV infection provided the ability to identify carriers of that agent. . . . Evidence that contact is sometimes a basis for transmission from person to person has caused Type B hepatitis to be regarded by many as highly contagious. . . . There have been word-of-mouth reports of frightening consequences for health-care personnel discovered through one or another circumstance to have chronic infection. . . . Clearly, a major problem has emerged.

"... It is necessary to conclude . . . that there is some risk of transmission.

### 'The Tip of an Iceberg'

"Do the few incidents in which transmission has been recognized represent very unusual occurrences, or could they be merely the tip of an iceberg? Alter and his associates report that two members of the staff at the Clinical Center, NIH, did not cause 57 patients with whom they had contact in the late incubation period to have risk exceeding that of a control group. Similarly, Williams and his co-workers found that two dentists did not produce hepatitis among 237 patients. . . .

"This information . . . is not necessarily applicable to the risk posed by carriers. It is in this regard that Alter and his colleagues have made their more valuable contribution. The NIH group observed 171 Clinical Center patients for whom three staff members, two physicians and a nurse, provided care. No excess frequency of HBV infection was associated with this carrier contact. As they point out, the proportion of carriers for which their negative result is descriptive is still not known. They have demonstrated, however, that carriers are not necessarily a source of contagion.

"Whatever the cost to individuals, the institutions with which they are associated, or their communities, carriers implicated as a likely source of infection for patients should be excluded from direct care. One should not categorically exclude all carriers, however, until there is evidence that this step is actually necessary. . . . It should be recalled that the segregation of lepers was found to be epidemiologically unjustified only after countless lives had been ruined; close and prolonged contact is necessary to transmit leprosy. Let us be certain we do not make a similar mistake. . . ." (Editorial, James W. Mosley, M.D., New Eng. J.M. 292:477, Feb. 27, 1975)

## SLEEPING BETTER...

## THE BEGINNING OF THE END OF CLINICAL DEPRESSION/ANXIETY

Even before it helps her clinical depression/anxiety, Sinequan® (doxepin HCl) can help her sleep through the night.

The sedative effect of Sinequan usually helps clinically depressed/anxious patients with accompanying sleep disturbances fall asleep more easily, remain asleep, and awaken more rested.

Administering the major portion of the daily dose *h.s.* generally obviates the use of supplementary hypnotic agents.

The marked anxiolytic property of Sinequan is particularly helpful in relieving apprehension, tension and worry. Optimal antidepressant effect is usually seen two to three weeks after initiation of therapy.

# SINEQUAN®

## DOXEPIN HCl

10 mg, 25 mg, 50 mg and new 150 mg capsules

### BRIEF SUMMARY

#### Sinequan® (doxepin HCl) Capsules

**Contraindications.** Sinequan is contraindicated in individuals who have shown hypersensitivity to the drug.

Sinequan is contraindicated in patients with glaucoma or a tendency to urinary retention.

**Warnings.** *Usage in Pregnancy:* Sinequan has not been studied in the pregnant patient. It should not be used in pregnant women unless, in the judgment of the physician, it is essential for the welfare of the patient, although animal reproductive studies have not revealed in any teratogenic effects.

*Usage in Children:* The use of Sinequan in children under 12 years of age is not recommended, because safe conditions for its use have not been established.

**MAO Inhibitors:** Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with Sinequan (doxepin HCl). The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

**Precautions.** Since drowsiness may occur with the use of this drug, patients should be warned of that possibility and cautioned against driving a car or operating dangerous machinery while taking this drug.

Patients should also be cautioned that their response to alcohol may be potentiated. Since alcohol is an inherent risk in any depressed patient and may remain so until

significant improvement has occurred, patients should be closely supervised during the early course of therapy.

Although Sinequan (doxepin HCl) has significant tranquilizing activity, the possibility of activation of psychotic symptoms should be kept in mind.

Other structurally related psychotherapeutic agents (e.g., iminodibenzyl and dibenzocycloheptenes) are capable of blocking the effects of guanethidine and similarly acting compounds in both the animal and man. Sinequan, however, does not show this effect in animals. At the usual clinical dosage, 75 to 150 mg. per day, Sinequan can be given concomitantly with guanethidine and related compounds without blocking the antihypertensive effect. At doses of 300 mg. per day or above, Sinequan does exert a significant blocking effect. In addition,

Sinequan (doxepin HCl) was similar to the other structurally related psychotherapeutic agents as regards its ability to potentiate norepinephrine response in the animal. However, in the human this effect was not seen. This is in agreement with the low incidence of the side effect of tachycardia seen clinically.

**Adverse Reactions, Anticholinergic Effects:** Dry mouth, blurred vision, and constipation have been reported. They are usually mild, and often subside with continued therapy or reduction of dose.

**Central Nervous System Effects:** Drowsiness has been observed. This usually occurs early in the course of treatment, and tends to disappear as therapy is continued.

**Cardiovascular Effects:** Tachycardia and hypotension have been reported infrequently. Other infrequently reported side effects

include extrapyramidal symptoms, gastrointestinal reactions, secretory effects such as increased sweating, weakness, dizziness, fatigue, weight gain, edema, parosmia, flushing, chills, linitis, photophobia, decreased libido, rash, and pruritus.

**Dosage.** For most patients with illness of mild to moderate severity, a starting dose of 25 mg. t.i.d. is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg./day to 150 mg./day.

In more severely ill patients an initial dose of 60 mg. t.i.d. may be required with subsequent gradual increase to 300 mg./day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg./day.

In patients with very mild symptomatology

or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg./day.

Although optimal antidepressant response may not be evident for two to three weeks, anxiolytic activity is rapidly apparent. Supply. Sinequan (doxepin HCl) is available as capsules containing doxepin HCl equivalent to 10 mg., 25 mg., 50 mg., and 100 mg. of doxepin in bottles of 100, 1000, and unit-dose packages of 100 (10 x 10's).

More detailed professional information available on request.

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## Abortions Not Up In Asthmatics on Corticosteroids

Medical Tribune Report

SAN DIEGO, CALIF.—The rate of spontaneous abortions in pregnant asthmatics treated with corticosteroids appears to be no higher than what would be expected in the general population, according to a team of researchers from the Northwestern University School of Medicine. Earlier studies indicated that corticosteroids do cause an increased incidence of abortions in animals.

Of 70 pregnancies observed in 55 asthmatics receiving corticosteroid therapy, only one terminated in spontaneous abortion, Dr. Michael Schatz told the 31st Annual Meeting of the American Academy of Allergy here. In addition, there were no maternal, neonatal, or fetal deaths and no increased incidence of toxemia, uterine hemorrhage, or congenital malformations, the Northwestern study showed.

"Except for a somewhat increased incidence of prematurity in our patients, there is no evidence of significantly more complications of pregnancy or fetal outcome in the present series than one would expect in the general population. The reason for the increased incidence of prematurity in this series is unclear, but inasmuch as it was not associated with persistent fetal abnormalities or loss, it would appear to be less significant," Dr. Schatz said.

### Anoxia Seen Greater Hazard

"One pregnancy terminated in spontaneous abortion at ten weeks, an incidence of 1.4 per cent," he said. "The patient was not on steroids at conception and received an average of 8.8 mg. of prednisone per day before the steroids were discontinued sixteen days prior to the abortion. The abortion was apparently preceded by increasing asthma not treated with steroids.

"Based on the information reported here, we consider the risk of maternal and fetal anoxia associated with severe asthma a greater potential hazard than the judicious use of corticosteroids during pregnancy."

The study, which is the largest analysis of asthmatics treated with corticosteroids during gestation yet reported, was based on medical records compiled at Northwestern University, the University of Washington and several other medical centers throughout the country.

Collaborating with Dr. Schatz were Drs. Roy Patterson, Stanley Seitz, John O'Rourke and Howard Melam.



"Doctor, the people who take geriatric medications—don't they age without them?"

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## IN CONSULTATION

## What's new and important in puberty studies?

## Part II



## The Consultant

DR. ALLEN W. ROOT

Director, University Service,  
Professor of Pediatrics,  
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St. Petersburg, Fla.

What are the important clinical points to observe in evaluating a patient with delayed sexual maturation and what studies are available to help differentiate between constitutional delay in growth and development and hypogonadal states?

Girls who have undergone no adolescent changes by 13 years of age and boys by 14 years should be evaluated for delayed sexual maturation. Delayed sexual maturation may reflect merely a slow rate of adolescent development which is a variation of the normal (constitutional) delay in growth and development.

In children with suboptimal nutrition (who are underweight for their height) delay in growth and sexual maturation is common. Disorders of the hypothalamus, pituitary and gonads as well as chronic systemic diseases are associated with delayed sexual development.

When evaluating such a patient the personal and family histories should be thoroughly reviewed with attention to the linear growth and weight gain patterns of the patient and the history of sexual development in siblings, parents, aunts and uncles. Past history of medical illnesses, trauma (particularly to the head), eating habits and patterns of weight gain should be recorded. The family history may reveal relatives with similar patterns of delayed growth and development.

## Linear Growth Patterns

The child with constitutional delay will have a normal linear growth velocity in a height channel between the third and tenth percentiles or slightly below the third percentile but maintaining a position parallel to the norm. In children with serious organic diseases (deficiency of pituitary function, hypothyroidism, chronic diseases of the cardiovascular, respiratory, urinary and gastrointestinal systems) the linear growth pattern will often reveal progressive deviation away from the normal channel.

In girls the earliest sign of puberty is an increase in the linear growth velocity. Physical examination is extremely important and should include: recording of height, weight, span, lower limb length and blood pressure, evaluation of the general physical status, a search for systemic abnormalities and determination of the stage of sexual maturation. Thorough neurological funduscopic and visual field examinations should be performed.

The earliest sign of puberty in the boy is testicular enlargement, while in girls breast budding is most frequently the first physical sign of adolescence. In younger boys very small testes may

suggest a primary testicular abnormality (Klinefelter's syndrome) while in older males gynecomastia and a eunuchoid body habitus are also present. Some subjects with Klinefelter's syndrome may be significantly virilized. In patients with gonadotropin and growth hormone deficiencies the testes may also be small. In girls with delayed adolescence stigmata of gonadal dysgenesis (Turner's syndrome) should be sought: short stature, webbed neck, characteristic facies, shield chest, hypoplastic nipples, increased carrying angles, increased numbers of nevi and history of edema of the dorsum of the hands and feet.

If the historical review and physical examination do not provide specific diagnostic leads the following studies are undertaken:

1) bone age determination: in pa-

tients with constitutional delay in growth and development, height and bone ages are usually equally retarded behind, but more than 75 per cent of chronologic age;

2) skull x-ray will provide information concerning the size of the sella turcica, perisellar calcification and intracranial pressure;

3) buccal smear examination should be done in all girls with delayed adolescence and if there is any clinical suspicion of gonadal dysgenesis chromosome karyotyping should be performed. Occasionally laparoscopy and direct visualization and biopsy of the ovaries may be required;

4) measurement of serum LH and FSH concentrations is of aid in identifying the subject with hypergonadotropic hypogonadism but may not distinguish between patients with hy-

# after taking a potent analgesic 360 times in 360 days



gonadotropic hypogonadism and constitutional delay in development;

5) the LH secretory response to Gn-RH will identify the latter subject who will have a prepubertal but definite increase in LH levels following Gn-RH administration, while the subject with hypogonadotropic hypogonadism will often have undetectable levels of LH before and after stimulation. Prolonged administration of Gn-RH eventually stimulates LH secretion in many subjects with hypogonadotropic hypogonadism indicating that in most instances this abnormality resides primarily within the hypothalamus;

6) measurement of plasma levels of testosterone or estradiol document gonadal function. Direct estimation of testicular responsiveness may be performed by measuring plasma testosterone concentrations before and after

administration of human chorionic gonadotropin (hCG) (2000 units i.m. for three days);

7) ancillary studies of endocrine function (assessment of growth hormone, thyrotropin secretion), and of other systems should be performed as indicated.

What are the recommended approaches to therapy in these conditions, and the best time to start?

In patients with primary hypogonadism (abnormalities of the testes or ovaries) therapy should be started at the usual age of puberty. In boys with Klinefelter's syndrome, anorchia or other forms of testicular dysfunction, treatment with testosterone (testosterone enanthate 50-100 mg. intramuscularly monthly or methyltestosterone 10-20 mg. orally daily) should be initiated at 13 years of age or as soon thereafter as the diagnosis is established even if there is evidence of endogenous androgen secretion in order to ensure more adequate physical and psychosocial maturation and to prevent development of the eunuchoid body habitus. In girls with gonadal dysgenesis estrogens may be initiated at 13 years, although some physicians prefer to begin treatment at 15-16 years in order to permit maximal attainment of linear growth prior to estrogen-induced epiphyseal fusion.

In this writer's opinion treatment should not be delayed at the expense of significant emotional trauma to the patient who invariably compares her state of breast and adolescent development with that of her peers. In this instance adolescent sexual development

## Next In Consultation

DR. JAY N. COHN, Professor of Medicine, Head, Cardiovascular Section, University of Minnesota Hospital, Minneapolis, Minn.

... will discuss what's new and important in the management of heart failure and the application of long-term vasodilator therapy in chronic congestive heart failure, the use of nitroglycerin in acute myocardial infarction, and the place of norepinephrine, isoproterenol and other beta-adrenergic stimulatory drugs in cardiogenic shock. He will also discuss the current status of intra-aortic balloon counterpulsation in cardiogenic shock in acute myocardial infarction.

compensates for the sacrifice of several millimeters of height. Ethinyl estradiol (0.05-0.1 mg. orally in cycles of 21 days on, 7 days off) or estradiol benzoate (1-2 mg. intramuscularly monthly) will usually be sufficient to feminize the child. Progesterone may be added to the regimen later if breast development is insufficient or if menstrual flow is "ragged". The use of synthetic androgens has been advocated in order to increase height in children with gonadal dysgenesis. There are no convincing data to indicate this treatment is of benefit.

In adolescents with hypogonadotropic hypogonadism treatment with gonadal sex hormones is indicated to bring about secondary changes of puberty. Some workers may prefer to employ gonadotropins (hCG, human menopausal gonadotropins) in these patients but this writer defers the use of gonadotropins until fertility is desired. The use of Gn-RH in these patients has not been fully evaluated but may prove to be most physiologic method of treatment.

## A Treatment Controversy

There is controversy concerning the treatment of the boy with constitutional delay in growth and adolescent maturation. The majority of these boys and their families are helped by assurance that the boys are normal and that puberty will occur, although at a later age than in the average boy. On occasion positive benefit may be anticipated by treating a boy with constitutional delay in sexual maturation if that boy is exceptionally disturbed by his body image relative to that of his peers. In these instances testosterone enanthate or methyltestosterone employed intermittently with frequent clinical assessment and bone age determinations may be employed.

Care must be taken to be certain that undue acceleration of skeletal maturation does not occur. It must be emphasized that the object of treatment is only to accelerate the rates of linear growth and sexual maturation and that treatment is terminated when there are signs (testicular enlargement) of activity of the patient's hypothalamic-pituitary-gonadal axis. HCG may also be used in such boys.

Some authorities advocate the liberal use of androgens in boys with constitutional delay, but this writer prefers to reserve therapy for those boys with marked delay who are deeply disturbed by their immature physical appearance.

Continued on page 15

## how big a dose will now bring relief if it is a narcotic?

"Tolerance is an ever-present hazard to continued use of narcotics. The very first dose diminishes the effects of subsequent doses." And, as increasing amounts of narcotics are required to control pain, distressing adverse effects—lethargy, hypotension, constipation, etc.—can needlessly debilitate the patient.

I. Sedova, M. S., A look at narcotic and non-narcotic analgesics, Postgrad. Med. 49:102, June 1971.

## how big a dose will now bring relief if it is Talwin?

Chances are, the same 50 mg. Talwin Tablet you prescribe originally will continue to provide good pain relief. Talwin can be compared to codeine in analgesic efficacy: one 50 mg. tablet appears equivalent in analgesic effect to 60 mg. (1 gr.) of codeine. However, patients receiving Talwin Tablets for prolonged periods face fewer of the consequences you've come to expect with narcotics. There should be fewer "adverse effects" on her way of life.

**Tolerance rare:** Tolerance to the analgesic effect of Talwin Tablets is rare.

**Dependence rare:** During three years of wide clinical use, there have been a few reports of dependence and of withdrawal symptoms with orally administered Talwin. Patients with a history of drug dependence should be under close supervision while receiving Talwin orally.

**In prescribing Talwin for chronic use,** the physician should take precautions to avoid increases in dose by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.\*

**Generally well tolerated by most patients:** Infrequently causes decrease in blood pressure or tachycardia; rarely causes respiratory depression or urinary retention; seldom causes diarrhea or constipation. Acute, transient CNS effects, described in product information, have occurred in rare instances following the use of Talwin Tablets. If dizziness, lightheadedness, nausea, or vomiting is encountered, these effects may decrease or disappear after the first few doses.

\*See important product information for adverse reactions, patient selection, prescribing and precautionary recommendations.

in chronic pain  
of moderate to severe intensity  
**Talwin® 50 mg. Tablets**  
brand of  
**pentazocine**  
(as hydrochloride)

Talwin® Tablets brand of pentazocine (as hydrochloride)

Analgesic for Oral Use —

Indications: For the relief of moderate to severe pain.

Contraindications: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: Drug Dependence. There have been instances of psychological and physical dependence on pentazocine in patients with a history of drug abuse and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of pentazocine has resulted in withdrawal symptoms. There have been a few reports of dependence and of withdrawal symptoms with orally administered Talwin. Patients with a history of drug dependence should be under close supervision while receiving Talwin orally.

In prescribing Talwin for chronic use, the physician should take precautions to avoid increases in dose by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain. Head injury and increased intracranial pressure. The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Further, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Use in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects.

Use in Children. Because clinical experience in children under 12 years of age is limited, administration of Talwin in this age group is not recommended. In children, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects. Patients receiving Talwin during labor have experienced no adverse effects.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is discontinued it should be done with caution since the acute CNS manifestations may recur.

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# "Let me tell you about the medicine I'm going to prescribe"

## TALKING OVER VALIUM®(diazepam) THERAPY WITH YOUR ANXIOUS PATIENT.



A patient often benefits by a greater understanding of his treatment program. You may find it helpful to make your patient aware that the purpose of therapy with Valium is to help reduce discomforting and disabling symptoms of excessive psychic tension and anxiety. It is beneficial for him to understand that much of his tension and anxiety can be relieved by your reassurance and counseling, and that these measures can do more than anything else to help him cope with his basic problems. The patient is reassured in knowing he can expect his medication to help him avoid feeling overwhelmed by his symptoms.

And it's also good for him to realize that he will be taking Valium only as long as he needs it.

Your expressed confidence in the medication prescribed, and the positive atmosphere in which therapy is given and accepted, work to the patient's advantage.

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follow my directions  
closely."*

*"I'll see you again the week  
after next and we'll see  
how you're making out."*

Your patient is often likely to feel reassured when you talk about seeing him again to check his progress. A planned visit evidences your continued interest and affords the patient an opportunity to report improvement he has made and to relate whatever continuing or additional difficulties he may be experiencing. It's also a chance for him to describe his response to therapy with Valium.

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## Valium® (diazepam)

2-mg, 5-mg, 10-mg scored tablets  
*for individualized treatment of psychic tension*

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Please see the following page for a summary of product information.



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2-mg, 5-mg, 10-mg scored tablets

**Prompt, effective action.** Valium (diazepam) works rapidly to relieve pronounced psychic tension in patients overreacting to stress and in psychoneurotic patients.

**Before prescribing, please consult complete product information, a summary of which follows:**

**Indications:** Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

**Contraindicated:** Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

**Warnings:** Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

**Precautions:** If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other anti-

depressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

**Dosage flexibility.** Scored Valium 2-, 5-, and 10-mg tablets give you dosage flexibility no tranquilizer capsule can match.

**Side Effects:** Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

**Dosage:** Individualize for maximum beneficial effect. **Adults:** Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. **Geriatric or debilitated patients:** 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) **Children:** 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

**Supplied:** Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500; Tel-B-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10.



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and Medical News  
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### On the Dispensing of Drugs

The best laid schemes o' mice and men gang aft a-gley.—Robert Burns

It would appear that a number of leaders in the pharmaceutical professions are leading their members into a terrible dead-end. As in *The Nutcracker Suite*, they are having visions of sugar-plum fairies—dreams of huge profits. These visions may lead their profession to disaster. Through brilliant and persistent lobbying, they may succeed in overturning a range of traditional patterns in the dispensing of drug prescriptions. Profit mark-ups will, in their plans, be displaced by fees; generic prescribing will replace specifications of particular manufacturers' drugs; anti-substitution laws will be repealed.

#### Major Drug Costs Lie in Distribution

There is a very conscious effort by some pharmacy leaders to bring about a redistribution of the prescription dollar—ostensibly in the interests of "economy"; practically, in the presumed economic interest of the pharmacist. What is overlooked by the proponents of some of these plans is the fact that fifty per cent or more of the prescription cost of a trademarked drug does not relate to its research, its raw materials, its manufacture, its product liability insurance or its promotion or scientific communication—but to its distribution. In respect to generic prescriptions, up to 80 or 90 per cent or even more may relate not to the cost of the drug but to the cost of its distribution. The drive for a fee structure may not significantly reduce the prescription price at the pharmacy but will increase the profit of the pharmacist—temporarily.

#### The Liability For Drug Disaster

To repeal the anti-substitution laws is a dangerous play as was tragically demonstrated by the "Russian roulette" involved in regard to potency variations of digitalis glycosides. Pharmacists as well as physicians would do well to recognize that in the present distribution system protection against drug disaster due to drug defects rests in the control sector of the manufacturer and liability falls on his shoulders. Aside from the large, major companies, very few of the small generic manufacturers would have the fiscal viability to survive and meet the costs of a drug disaster which would then fall upon the pharmacist and/or physician.

The inherent illogic of the drive to replace trademarked prescription drugs at the pharmacy by "cheap" generics is implicit in the false suggestion that a generic drug costs patients but a fraction of a trademarked drug. Untrue. If a shift to generics took place on this premise, retail pharmacists would face a financial disaster. That is the reason for the proposals for dispensing fees and that is also the Achilles heel of this plan of short range expediency and long range disaster.

#### Who Knows Best—Pharmacist or Physician?

The advocates of the dispensing fee say the pharmacists know more about drugs than physicians. Do they? Do they also know more about the patient, or the patient's diseases? They know less about these than the physician does and may know practically nothing about the physician's therapeutic objectives. It does not serve the professional pharmacist to restructure the distribution systems of drugs because such a development will not only reduce progress in the fields of therapeutics, in which he should be and is interested, but, worse for him, it will point a direction that can constitute economic disaster for pharmacy.

Members of our legislatures and of government agencies that are pressing for changes in present economic patterns of drug manufacture focus on presumed economic savings that they wish to achieve as part of their plan for either national health insurance or, ultimately, the nationalization of medicine. The pharmacists would do well to consider, "How long will the pharmacy retain economic independence if third party payments take over and/or if medicine is nationalized?"

#### Doctors' Dispensing May Save Hundreds of Millions

If economics is the sole issue in respect to drug prices, generic drugs and repeal of the anti-substitution laws, then consider the following: The greatest savings that can be made in respect to the cost of prescription drugs is not in the area of its research, of its control, of its promotion, and its production—the largest single element of cost in respect to a prescription drug is in its distribution. This is true for the trademarked drugs and even more true for the generic drug. It is inevitable that the government budget boys will soon see this and sharpen their pencils.

What will be the role of the pharmacist if the government and third party payers propose in the interest of economy that physicians dispense fifty or one hundred of their most frequent prescriptions—and do so at a dispensing fee of one dollar (not \$2.50) over cost? With one stroke this would achieve a savings of hundreds of millions of dollars. Moreover, it would save the patient the time necessary to go to the pharmacy to have the prescription filled. It would speed the therapeutic process and afford closer patient management.

#### Untested Systems May Be Dangerous

MEDICAL TRIBUNE does not believe it is in the interest of either the patient or the medical or pharmaceutical professions to destroy existing channels of distribution before other systems have either been tested or put into place.



"My God, that's my psychiatrist!"

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MEDICAL TRIBUNE believes it is potentially disastrous to gut anti-substitution laws whose repeal will inevitably be followed by dissatisfaction when the hypothetical savings that are promised do not materialize and when preventable drug disasters ensue. MEDICAL TRIBUNE does not believe it wise to distort or destroy the present relationship between the professions of pharmacy and of medicine. MEDICAL TRIBUNE believes it would be disastrous to entice professional pharmacy for short term gains onto a path which can lead to its eventual economic and professional destruction. *No loosening of restrictions on pharmacists can long prevail at the cost of increasing restrictions on the physician.*

When pharmaceutical organizations

play a political game pitting pharmacists and pharmaceutical manufacturers against each other and pharmacists against doctors and, ultimately, doctors against both the pharmacists and the manufacturers, they play with fire. They are exposing their constituencies to the dangers of government economy measures in the areas of prescription drugs which at the very least would place increasing economic restrictions on pharmacists, or lead to the return of drug dispensing in the physician's office. Any actions contributing to increasing governmental economic regulation in the health care field will contribute ultimately to a nationalization of health services which will not be restricted to physicians but must inevitably encompass pharmacists as well. A.M.S.

### LETTERS TO TRIBUNE

#### Beck's Bypass Approach

I was personally very much interested in the article, "Bypass Grafts to Coronary Veins", (MT, Mar. 5). During my association with Claude Beck for over thirty years, I recall that he had carried out a saphenous graft by-pass from the aorta to the great vein of the base of the heart.

In the 1949-50 period, he had done several dozen on bull dogs. Following this in several separate operations or steps, he would completely ligate each main coronary artery near its origin.

In 1951, I was present when three dogs whose three main coronaries had previously been ligated were exposed and a clamp placed across the hypass. Much to our surprise, their hearts continued to beat. Later they were sacrificed.

After careful examination and perfusion, it was found that the septal branch of the coronary tree had enlarged and become the main source of the arterial blood to a beautifully developed collateral circulation. (Normally the dog has a relatively larger septal branch than the human).

During the period 1950-52 he must have performed this operation (he called it the Beck II) on 12-15 humans. At the same time he introduced an unique aortic clamp. He appeared to give up this phase of trying to improve the collateral circulation of the heart for two main reasons: (1) a number of the bypasses thrombosed; (2) co-incidentally, at the same time he temporarily lost his academic appointment.

The authors are to be complimented on their work and their refined approach.

ROBERT M. HOSLER, M.D.  
Cleveland, O.

#### Time-saving Questioned

Your front-page report (MT, Feb. 19) on the Pfizer produced Autobac I states that the new machine will shorten the waiting time for test results by one day as compared with the traditional Kirby-Bauer method.

This seems hardly possible, because in our laboratory the Kirby-Bauer method takes only 6-8 hours from start to the end. A culture available in the morning for testing will be done with by late afternoon. After 6 hrs. of incubation preliminary readings are available and at 8 hrs. the final report may be sent out.

There will be some time-saving with Autobac I, but it will be of only 2-4 hrs. In my general pediatric practice there has been not one instance in 1974 where such earlier availability of test results would have been needed or where it would have made any difference in patient management.

I believe that the investigators are too optimistic if they think that the nation may save up to 100 million dollars with the new \$19,000 laboratory machine. The instances where Autobac I will actually shorten the hospital stay will be few and far between.

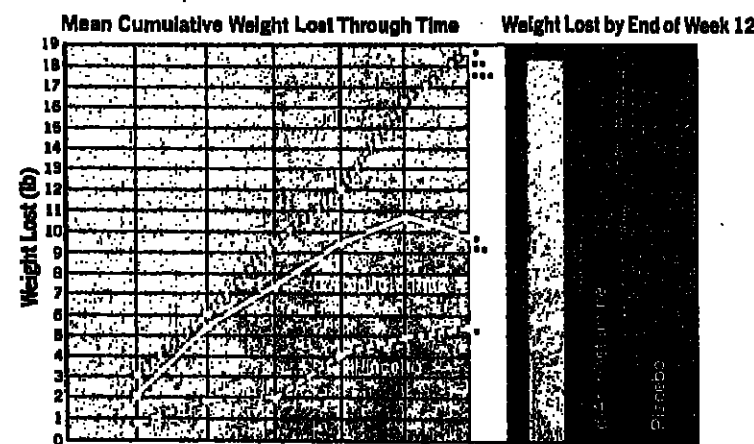
ALFRED W. BAUER, M.D.  
Kirkland, Wash.



**MAZINDOL® IN OBESITY**  
(MAZINDOL) TABLETS, 1 mg and 2 mg.

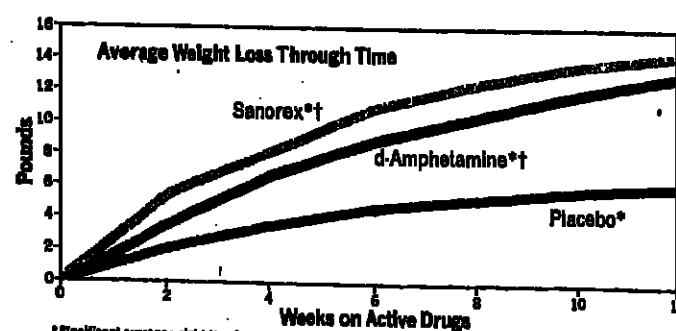
the soft underbelly  
of American health

## AS EFFECTIVE AS d-AMPHETAMINE



In a double-blind study<sup>1</sup> of 40 obese patients (all of whom completed the study), Sanorex (1 mg t.i.d.) was more effective than either placebo or d-amphetamine (5 mg t.i.d.) in helping patients lose weight.

The 14 patients on Sanorex experienced a substantially greater mean weight loss—1½ to 2 lb/wk, as compared with 1 to 1½ lb/wk for the 14 d-amphetamine patients—throughout the 12-week phase of active medication. After the sixth week, the superiority of Sanorex became increasingly evident. And as treatment progressed, so did weight loss in patients on Sanorex—whereas after the tenth week, patients on d-amphetamine began to regain some weight.



\* Significant greater weight loss from post-baseline level at each two-week interval (p<0.001).  
† Significantly greater average weight loss than with placebo at each two-week interval (p<0.001).

In a double-blind study<sup>2</sup> of 90 obese patients (59 of whom completed the study), Sanorex (1 mg t.i.d.) was more effective than either placebo or d-amphetamine (5 mg t.i.d.) in helping patients lose weight.

By the end of the third week of active medication, weight loss in the 20 d-amphetamine patients began to plateau, and by the end of the fifth week, these patients began to regain some weight. On the other hand, the 18 patients on Sanorex continued to lose weight throughout the six-week course of therapy.

In a double-blind study<sup>3</sup> of 93 obese patients (all of whom completed the study), 30 patients received Sanorex (1 mg t.i.d.), 31 received placebo, and 32 received d-amphetamine (5 mg t.i.d.).

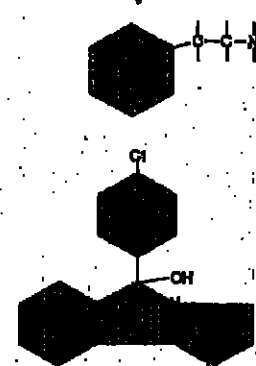
During the 12-week phase of active medication, patients on Sanorex lost an average of 14.1 lb, compared with 13.1 lb for d-amphetamine patients and 5.8 lb for placebo patients. Throughout the active medication phase, 63% of patients on Sanorex lost more than 1 lb/wk, compared with 38% of the d-amphetamine group and 29% of the placebo group.

## BUT WITH CERTAIN DIFFERENCES

Although the pharmacologic activity of Sanorex and that of amphetamines are similar in many ways (including central nervous system stimulation in humans and animals, as well as production

of stereotyped behavior in animals), animal experiments suggest that there are differences. Sanorex also differs in basic chemical structure from amphetamines and all other prescription anorexants.

### Different Chemical Structure



An important chemical similarity between amphetamines and all other prescription anorexants except Sanorex is the basic phenethylamine structure to which their differentiating chemical radicals are attached.

An important chemical difference between Sanorex and all other prescription anorexants is that Sanorex is an isoindole; it does not contain a phenethylamine structure.

### Different Neurochemical Action

**Action of d-Amphetamine** In animal studies, d-amphetamine (like intake of food) activates afferent neurons leading to appetite centers in the hypothalamus. Resulting release of norepinephrine activates the receptor neurons. Unlike food, however, d-amphetamine also suppresses norepinephrine synthesis. Thus, increasingly larger doses of d-amphetamine become necessary to produce an effect.\*

**Action of Sanorex (mazindol)** After intake of food stimulates the release of norepinephrine from the afferent neuron, Sanorex blocks its re-uptake without disturbing normal synthesis and release.\*

\*The significance of these differences for humans is uncertain.

### Simplicity and Flexibility of Dosage

Simple one-a-day dosage is facilitated by 2-mg tablets (taken 1 hour before lunch).

New flexibility (for the patient in whom 1 mg t.i.d. is preferred) is now facilitated by new 1-mg tablets (taken 1 hour before meals).

For Brief Summary, please see facing page.

Wednesday, April 2, 1975

MEDICAL TRIBUNE

13

## SANOREX® (MAZINDOL)®

**References**  
1. Kornhaber A: Problems and current concepts in the treatment of obesity. Scientific Exhibit presented at the New York State Academy of Family Physicians 25th Annual Scientific Convention, McLean, NJ, May 8-10, 1973.  
2. Defalco EA, Chaykin LB, Cohen A: Double-blind clinical evaluation of mazindol, dextroamphetamine, and placebo in treatment of exogenous obesity. Curr Ther Res 15:358-366, July 1973.  
3. Varnes BJ: Practical considerations for managing obese patients: Initial interview and follow-up treatment in the office. Scientific Exhibit presented at the American Medical Association, 27th Clinical Convention, Anaheim, Calif, Dec 1-4, 1973.

**Indication:** In exogenous obesity, as a short-term (a few weeks) adjunct in a weight reduction regimen based on caloric restriction. The limited usefulness of agents of this class should be measured against possible risk factors.

**Contraindications:** Glaucoma; hypersensitivity or idiosyncrasy to the drug; agitated states; history of drug abuse; during, or within 14 days following, administration of monoamine oxidase inhibitors (hypertensive crisis may result).

**Warnings:** Tolerance to many anorectic drugs may develop within a few weeks; if this occurs, do not exceed recommended dose, but discontinue drug. May impair ability to engage in potentially hazardous activities, such as operating machinery or driving a motor vehicle, and patient should be cautioned accordingly.

**Drug Interactions:** May decrease the hypotensive effect of guanethidine; patients should be monitored accordingly. May markedly potentiate pressor effect of exogenous catecholamines; if a patient recently taking mazindol must be given pressor amine agents (e.g., levarteterol or isoproterenol) for shock (e.g., from a myocardial infarction), extreme care should be taken in monitoring blood pressure at frequent intervals and initiating pressor therapy with a low initial dose and careful titration.

**Drug Dependence:** Mazindol shares important pharmacologic properties with amphetamines and related stimulant drugs that have been extensively abused and can produce tolerance and severe psychological dependence. Manifestations of chronic overdosage or withdrawal with mazindol have not been determined in humans. Abstinence effects have been observed in dogs after abrupt cessation for prolonged periods. There was some self-administration of the drug in monkeys. EEG studies and "liking" scores in human subjects yielded equivocal results. While the abuse potential of mazindol has not been further defined, possibility of dependence should be kept in mind when evaluating the desirability of including the drug in a weight-reduction program.

**Usage in Pregnancy:** In rats and rabbits an increase in neonatal mortality and a possible increased incidence of rib anomalies in rats were observed at relatively high doses. Although these studies have not indicated important adverse effects, the use of mazindol in pregnancy or in women who may become pregnant requires that potential benefit be weighed against possible hazard to mother and infant.

**Usage in Children:** Not recommended for use in children under 12 years of age.

**Precautions:** Insulin requirements in diabetes mellitus may be altered. Smallest amount of mazindol feasible should be prescribed or dispensed at one time to minimize possibility of overdosage. Use cautiously in hypertension, with monitoring of blood pressure; not recommended in severe hypertension or in symptomatic cardiovascular disease including arrhythmias.

**Adverse Reactions:** Most commonly, dry mouth, tachycardia, constipation, nervousness, and insomnia. **Cardiovascular:** Palpitation, tachycardia. **Central Nervous System:** Overstimulation, restlessness, dizziness, insomnia, dysphoria, tremor, headache, depression, drowsiness, weakness. **Gastrointestinal:** Dryness of mouth, unpleasant taste, diarrhea, constipation, nausea, other gastrointestinal disturbances. **Skin:** Rash, excessive sweating, clamminess. **Endocrine:** Impotence, changes in libido have rarely been observed. **Eye:** Long-term treatment with high doses in dogs resulted in some corneal opacities, reversible on cessation of medication; no such effect has been observed in humans.

**Dosage and Administration:** 1 mg three times daily, one hour before meals, or 2 mg per day, taken one hour before lunch in a single dose.

**How Supplied:** Tablets, 1 mg and 2 mg, in packages of 100.

Before prescribing or administering, see package circular for prescribing information.

MAZINDOL PHARMACEUTICALS, EAST HANOVER, N.J. 07936

## 30 Surveys Reported to Fail In Telling When to Do T&As

Continued from page 1

niques." Such a study is essential, he said, to answer whether T&As should be done, and if so, when.

In the past, Dr. Feldman said tonsillectomies have been performed for indications ranging from "routine removal" to "pigeon-breast" to "retarded mental development due to anoxemia." While physicians and surgeons have been more selective in recent years, he noted, T&As were being done in the province of Ontario in 1971 at the rate of 174 procedures per 10,000 children.

Dr. Feldman and his associates—Drs. W. Shaikh, E. Vayda, and B. Haynes—designed a point system to evaluate all the evaluation studies of T&A reported in the English literature in the last 50 years. Points were given for categories of study design, sample, accuracy of description of therapy, and precision of follow-up. Those studies that were most objective in these areas were awarded the most points while those studies that were poorly done, poorly documented, and reflected bias were given the fewest.

In the category of study design, for example, the highest score was given to a randomized design and the lowest to a descriptive one. In the "sample" category, the highest score was given to a

study in which the patients most closely represented the general population. For the description of illness before therapy, points were given on the basis of how well the symptoms were quantitated and if reproducible criteria were established for the selection of T&A on the basis of these symptoms.

Points were given in the therapy category if the operation was described and complications of surgery and anesthesia were noted. Description of follow-up was scored in terms of objectivity. When follow-up consisted of a questionnaire to parents, for example, it was given a low score because, Dr. Feldman said, this form of questionnaire has been shown to be "grossly inadequate." Further points were given for frequency of observation, objective documentation of physician findings, and relevant laboratory findings.

With this scoring system, an ideal study could score 34 points. But of the 29 studies the team assessed, the highest any one scored was 18 points. "Only one study scored more than 50 per cent of the ideal score. The remaining 28 studies scored less than 40 per cent," says Dr. Feldman. "We conclude, therefore, that none of the studies has conclusively proved whether T&A is beneficial or not."

## Moses Swick Honored



Dr. Moses L. Swick, discoverer of intravenous urography, was recently given the degree of Honorary Doctor of Medicine by the Free University of Berlin. Dr. Swick spent the years 1927-30 in Germany on a special fellowship from Mount Sinai Hospital, New York, and conducted much of his research there.

## Phonoangiography Gauges Carotid Stenosis

Continued from page 1

Identify patients who do not need such an examination and thus could cut down on the number of arteriograms performed.

In the Boston study, phonoangiograms were performed on 61 carotid bruits in 48 patients. All patients also underwent carotid arteriography, and artery measurements obtained by both methods were compared.

Bruit amplitude characteristically reached maximum intensity in the higher frequencies and then began a sharp decline, Mr. Gruber reported. The frequency at which this decline started was termed the "break frequency."

To be acceptable for analysis, intensity spectra were required to show a single clear break frequency, and the slope of the decline had to correspond to the theoretical distribution of turbulent flow. Of the 61 tests, 11 did not produce the pattern of a single clear break frequency and hence proved unusable.

### An Inverse Relationship

The investigators found that the diameter of the stenotic segment is inversely related to the break frequency, according to the following equation: the smallest diameter of the stenotic segment equals the peak systolic velocity distal to the stenosis divided by the break frequency.

In the 50 acceptable tests, the diameter of the stenotic segment as obtained by phonoangiography was compared with the diameter obtained by standard radiographic arteriography.

Using 500 mm/second as the value for peak systolic velocity, the differ-

ence between these two diameters was less than 1 mm in 73 per cent of the study cases with residual lumen of 5 mm or less, with a mean difference of  $\pm 0.69$  mm.

But even better correlation was achieved when an empirical relationship was determined between blood flow velocity and the bruit intensity, Mr. Gruber noted, since the flow of blood through the stenosis and the intensity of the bruit both decrease as stenosis becomes more severe.

Standard arteriograms and phonoangiographic studies analyzed with the

help of empirically derived (rather than assumed) flow velocity agreed to within 1 mm in 84 per cent of the case studies where the residual lumen was 5 mm or less, with a mean difference of  $\pm 0.52$  mm.

"We believe that phonoangiography is of clinical value now for assessment of carotid artery disease," Mr. Gruber said. "Studies are in progress to determine its usefulness in the diagnosis of femoral artery and aortic valve stenosis."

Other members of the joint research team are Drs. G. Duncan and G.S. Myers, and C.F. Dowey, Jr. Ph.D.

## Abidjan Parley on Sickle Cell Anemia Finds U.S., African Approaches Vary

Medical Tribune World Service

ABIDJAN, IVORY COAST—Physicians attending an international symposium here on sickle cell anemia found there are some substantial variations in approach to the disease between Africa and the United States. These differences are seen both in clinical management of the disease and in genetic counseling aimed at preventing it.

Dr. Charles F. Whitten of Wayne State University told MEDICAL TRIBUNE that Africans "don't accord counseling the same high priority that we in the United States do at the moment, chiefly because they don't have the money for detection and counseling." Also, he said, the sickle cell patient seen in Africa tends to be suffering from multiple health problems, rather than sickle cell disease only.

Dr. Whitten added that he feels the conference, which drew participants from North and South America,

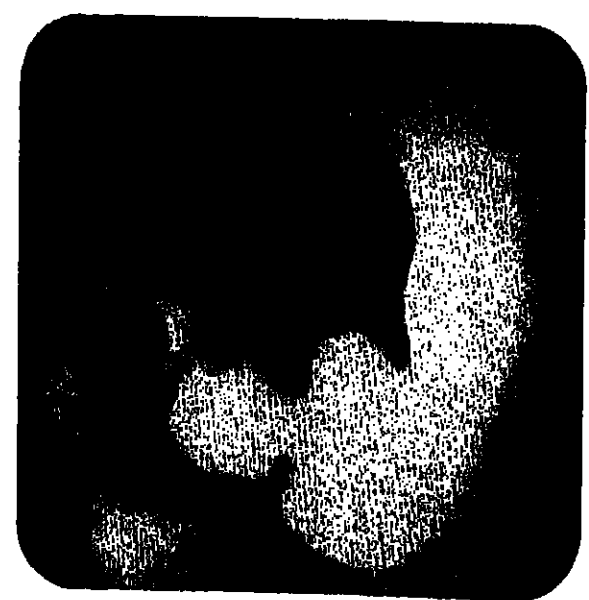
Europe, and Africa, "gave us a good opportunity to exchange experiences and to compare where we are."

Another American who attended, Dr. Charles M. Peterson of Rockefeller University, also noted the difference in clinical practice. "About 25 per cent of the sickle cell patients we see are usually suffering from an additional problem," he told MEDICAL TRIBUNE. "But in Africa, you can almost assume that a patient with sickle cell anemia has malaria plus several other infections."

Dr. Paul F. Milner, of the Center for Disease Control, saw yet another difference, one imposed by different systems of health care. "In this country," Dr. Milner told MEDICAL TRIBUNE, "we find most of our sickle cell patients in the big cities. In Africa, a lot of patients are being treated in the urban areas, but I think a large part of the patient population may still be in the rural areas."

## The Upper Functional G.I. Disorder

# The Pseudo-ulcer



## Ulcer-like symptoms: no G.I. pathology

The patient is convinced it's an ulcer. However, symptoms are not quite typical, and x-ray findings are negative. These findings and the results of additional diagnostic procedures exclude an organic basis for the patient's complaints. A diagnosis of "upper functional gastrointestinal disorder" is made, which is supported by the fact that episodes of painful symptoms coincide with episodes of excessive anxiety, as indicated by the history.

It may be useful to explain to the patient the mechanism by which emotions upset normal G.I. functioning, resulting in hypersecretion and hypermotility and thus causing such symptoms as nausea and epigastric pain. In upper functional gastrointestinal disorders, counseling by the primary physician can often help the patient to understand how excessive anxiety may cause flare-ups of G.I. symptoms.

A disproportionate number of patients seen by the general practitioner suffer from functional disorders, as do more than half of those seen by the gastroenterologist.\*

\*Where milder cases may respond to counsel-

ing alone, if symptoms are severe and disabling to any degree, a suitable regimen may include medication to reduce the symptoms and the excessive anxiety that often provokes these distressing symptoms.

In these cases, Librax as an adjunct can greatly contribute to the course of therapy. Its dual action can offer relief of both painful symptoms and excessive anxiety, because each capsule contains 5 mg chlorthalidone HCl and 2.5 mg clidinium Br. The antianxiety action of Librium® (chlorthalidone HCl) makes Librax exceptional among drugs for certain gastrointestinal disorders associated with excessive anxiety; the clidinium bromide (Quarzan™) component furnishes dependable antispasmodic action. Dosage is flexible; it may be adjusted according to your patient's requirements within the range of 1 or 2 capsules three or four times daily, up to 8 capsules daily in divided doses.

\*Rome HP, Brannick TL: Orientation and mechanism of functional disorders: Clinophysiology correlation, chap. 133, in *Gastroenterology*, edited by Dockus HL. Philadelphia, WB Saunders Company, 1965, p. 1116

An adjunct  
in anxiety-related upper  
functional G.I. disorders

## Librax®

Each capsule contains 5 mg chlorthalidone HCl and 2.5 mg clidinium Br.

pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards. As with all anticholinergic drugs, an inhibiting effect on lactation may occur.

**Precautions:** In elderly and debilitated, limit dosage to smallest effective amount to preclude development of ataxia, overexcitation or confusion (not more than two capsules per day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potent sedatives such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

**Adverse Reactions:** No side effects or manifestations not seen with either compound alone have been reported with Librax. When chlorthalidone hydrochloride is used alone, drowsi-

ness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible. In most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in ECG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally with chlorthalidone hydrochloride, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax are typical of anticholinergic agents, i.e., dryness of mouth, blurring of vision, urinary hesitancy and constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

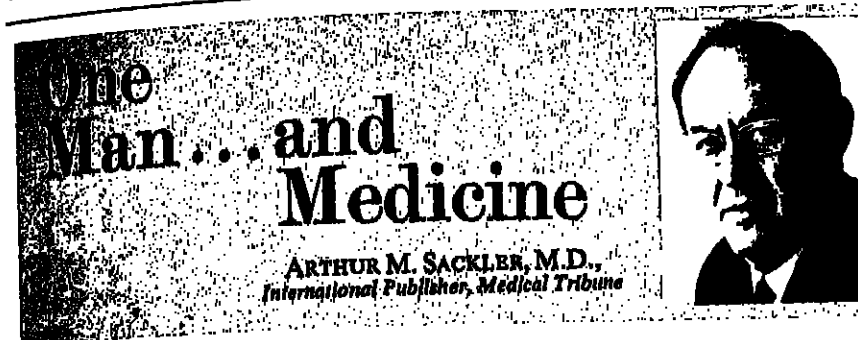


Roche Laboratories  
Division of Hoffmann-La Roche Inc.  
Nutley, New Jersey 07110

Wednesday, April 2, 1975

MEDICAL TRIBUNE

15



## Of Time and Life—Part I

"A rose is a rose is a rose."

LIFE'S TANGLED tracks crisscross and overlap. I was in Paris with Peter. Peter was American, a reporter and our French correspondent. As usual we discussed "business" as we went the round of exhibitions. It was after World War II. There was a retrospective of Picasso's paintings at the Museum of Decorative Arts. "This time, Arthur," said Peter, "you can't duck out. I have told Alice Toklas about you so often. She wants to meet you. You'll have to take the time."

Time, as you may have gathered by now, is my greatest enemy. Time, not oil, is man's most scarce resource. Time is a vicious dictator, inflexible, inexorable—and ultimately always the victor. Because of time, its lack, I missed meeting Gertrude Stein. Because of time, I missed Picasso (I will tell you about that some other time). "Okay, Peter, to hell with deadlines. Let's go."

### Of Sound and of Rhythm

Gertrude Stein was a quintessential American spirit. "A rose is a rose is a rose" is no nonsense rhyme. It is the celebration of American English. A rose is more than color, more than smell, more than form. It is the beauty of our language, of sound and of rhythm. I must tell you the story of the Spaniard praising the beautiful sound of English to an American. "Beautiful, like what?" asked the American. "Oh, the beauty of 'sella d'or'," ecstaticized the Spaniard.

"What was that?"

"Sella d'or."

"Write it out."

"Oh, you mean 'cellar door'."

Gertrude Stein, the ultimate intellectual, was a classical if not corny American in almost every conceivable way—her rebellious spirit and personal dress, her unorthodox insights and her derogation of sham. This unashamed, self-confessed giant of a mind, who accepted the intellectual and creative talents of very few as genuine (only such as Picasso and Whitehead), loved the song, *The Trail of the Lonesome Pine*. She unabashedly adored the genuineness of the doughboys of the first World War and the GIs of the second. Gertrude Stein loved America, she loved our language. All her writings rejoiced in the beauty of American speech and thought, American adventure and directness. But more about this on another occasion. Time is the problem here again.

### Back to Gertrude

Oh, yes, what has Gertrude Stein got to do with *One Man and Medicine*? If there ever was one Lady in Medicine who really had an impact on history, it was Gertrude Stein.

When I came into Alice Toklas' apartment, I saw a little old lady surrounded by the "modern" glories of

the Gertrude Stein collection in an "ancient" apartment. "Tell me about 1906 and 1907. There seems to be an acute and sharp break in the Picasso retrospective. A new vision opened with a simple painting which looked to me like a diaper hanging on a line." In those days I was still in the full flush of "febrile" psychanalytic interpretation. To me that picture signified rebirth.

### Exchange of Paintings

Alice Toklas said Picasso was wrestling with new ideas. Her recollections were a bit different than those of Gertrude Stein, as they were in regard to a number of other events. After Picasso and Matisse were introduced to each other, Gertrude Stein said, "They exchanged pictures as was the habit in those days." Each painter chose one of the other's that presumably interested him the most, but these "friends" did not necessarily pick the best one and "used it as an example . . . of the weakness of the other one." This is not the way Alice Toklas remembered the happening. Alice said that after a number of exchanges of paintings, Gertrude said to Picasso, "Pablo, you are a pig. Henri [Matisse] gives you some of his best paintings and you give him your worst." Picasso replied, "He shouldn't be a fool."

I remember at a retrospective of Matisse in the Museum of Modern Art in Paris, I was stunned to discover that the most beautiful Matisse paintings there were almost invariably from Picasso's personal collection. So I concluded that Alice Toklas had the story straight. Alice Toklas couldn't resist the opportunity to take a poke at the establishment. "You know," she remarked, "when the curators were here to select paintings for Picasso's retrospective, they originally passed up some of Pablo's best Cubist paintings. 'Oh,' they said, 'you have some Braques.'" Those Cubist Picasso's are, of course, and always will be some of the most beautiful manifestations of art. They represent the flowering of Spanish genius, grow-

ing in the soil of France where it was lovingly tendered by an American physician.

That day we talked quite a bit about Cubism. The fire of debate as to its origin still glowed. Gertrude Stein had claimed that the two closest influences on Picasso in the creation of Cubism were not African art but late Cezanne and actual Spanish landscapes. The Spanish villages which Picasso had recently visited were typical—they cut into and did not follow the landscape. The colors of early Cubism as you will recall were yellows, beiges and faint greens. Stein said that these were typical of the Spanish landscape. For Gertrude Stein, Cubism, real Cubism, was Spanish Cubism, the Cubism of Picasso and Juan Gris.

### Influence of African Sculpture

It would be nice if there were always a simple unity of cause. I've had some Picasso drawings and studied some of his sketches for the *Demise of the Avignon*. There is, for me, particularly in the heads, as well as bodies, not just Spanish landscape but African sculpture as well. Who am I to say whether the influence was direct or indirect, whether it was African sculpture or Spanish architecture and art. I enjoy my opinions\* but you may prefer the first-hand reports of Gertrude Stein, the American physician who, as a medical student, had delivered babies of the poor in Baltimore, and later in Paris was midwife at the birth of so much of the then reviled and now admired classics of modern art and aesthetics.

\*My feeling may not be so far out. Gertrude Stein, in acknowledging the impact of African statues on the School of Paris, noted that Matisse, who was the first to be influenced in his sculpture, "drew Picasso's attention to it."

## Cases of Hydatid Disease Rise in Canada and U.S.

Medical Tribune World Service

WINNIPEG, MAN.—Hydatid disease, a parasitic condition most often seen among sheep-raising peoples, is being seen with increasing frequency in Montreal, Dr. Nathan M. Sheiner told the Royal College of Physicians and Surgeons of Canada here.

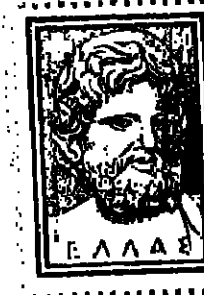
Twenty hydatid disease patients have been treated at the Montreal Jewish Hospital in the past 11 years, he said, 15 of them in the past five years. He noted that all have been immigrants—11 from Greece, five from the Middle East, and one each from Italy, Spain, Portugal, and Armenia.

In the United States, there has also been an increase in cases, according to reports from the Center for Disease Control in Atlanta. Previously, the C.D.C. said, cases had been confined to a few areas in California and Oregon. The new cases are being seen among Indian sheep-herding tribes in the Southwest. A C.D.C. spokesman said efforts to halt the disease are largely educational.

He recommended that the diagnosis of hydatid cyst be considered in every patient who comes from a geographical area where hydatid disease is endemic, and who presents with abdominal pain, jaundice, hepatomegaly, abdominal mass, or a pulmonary mass lesion.

## Medicine on Stamps

Aesculapian



In Greek mythology, Aesculapian was the son of Apollo and Coronis, received his medical education from the centaur Chiron, and was killed by Zeus with a thunderbolt because Pluto complained that through his great medical skill, Hades was being depopulated. In real life, Aesculapian, born about 1300 B.C., was apparently a renowned physician of Thessaly.

Text: Dr. Joseph Klar  
Stamp: Minkus Publications, Inc., New York

### Continued from page 7

Although constitutional delay in development is recognized less frequently in girls than boys, this may be due to more ready cultural acceptance of the immature girl. In such girls therapy is usually withheld, although at times the administration of estrogens may be warranted.

What is the acceptable treatment today of true sexual precocity, and what can be expected with the treatment?

There is no satisfactory treatment for idiopathic true, complete sexual precocity. Boys with sexual precocity should be evaluated periodically with neurologic and ophthalmologic examinations and skull roentgenograms to be certain not to overlook an intracranial neoplasm not manifest originally. If no underlying cause of the sexual precocity is found the parents should be reassured.

The patient should be dressed in loose fitting clothes, and every precaution must be taken to protect the child from unscrupulous individuals. Medroxyprogesterone (MPA) has been employed to treat children with sexual precocity. In girls MPA may interrupt menses and cause regression of the breasts.

However, this drug has no effect upon rapidly advancing skeletal maturation and has many side effects including aberrations of adrenal function, weight gain and fluid retention, alteration of chromosome morphology and prolonged suppression of the hypothalamic-pituitary axis.

It is not approved by the Food and Drug Administration for this purpose. In selected patients its use may be justified, however. Eventually children with sexual precocity become less obvious as their peers achieve sexual maturation. However, children with sexual precocity become short adults as there is premature fusion of the epiphyses.

### EPIGRAMS—Clinical and Otherwise

In medicine, sins of commission are mortal, sins of omission venial.

Theodore Tronchin (1709-81)

Quoted in *Bulletin of New York Academy of Medicine*, V (192)



# We know Librium works. (chlordiazepoxide HCl)

## We're still learning more about how and why.

### Value of continuing animal research

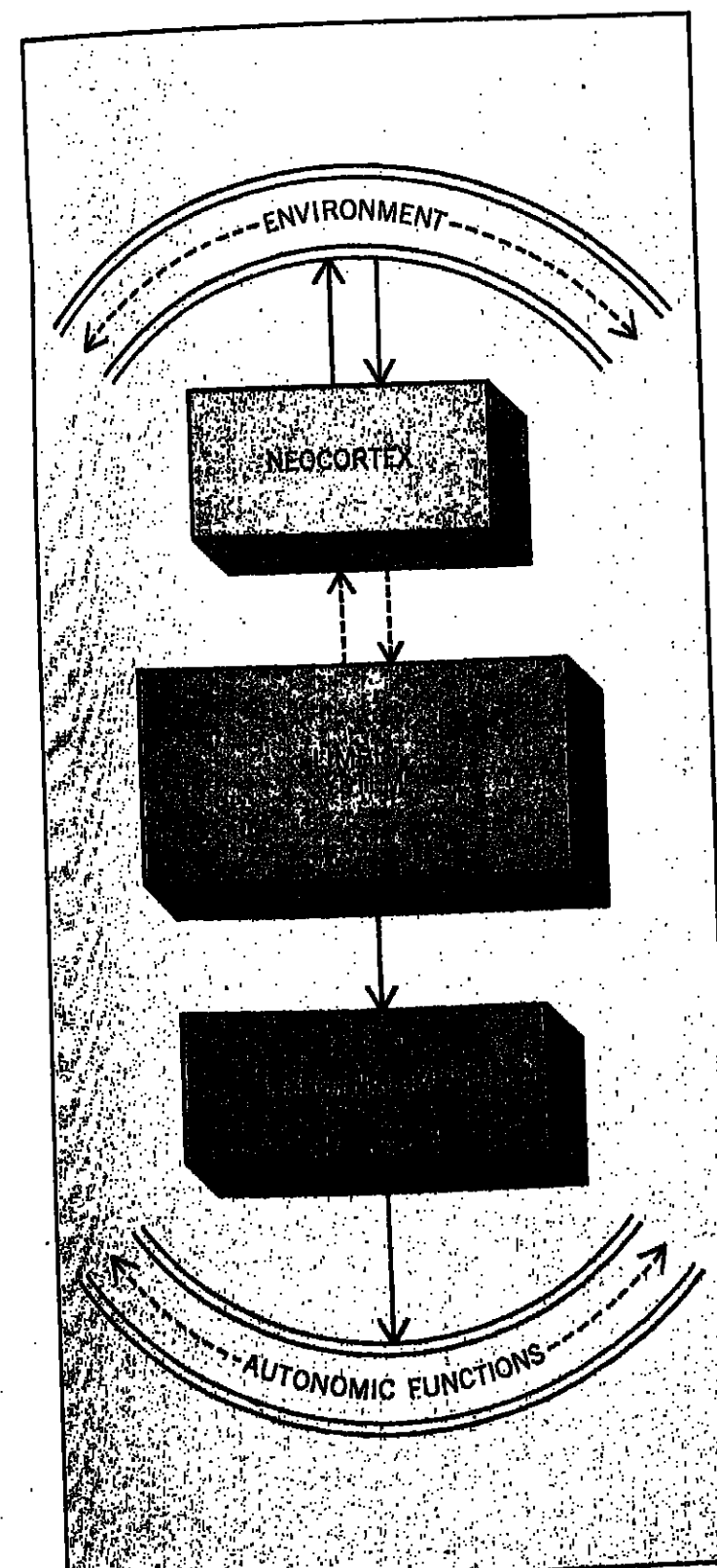
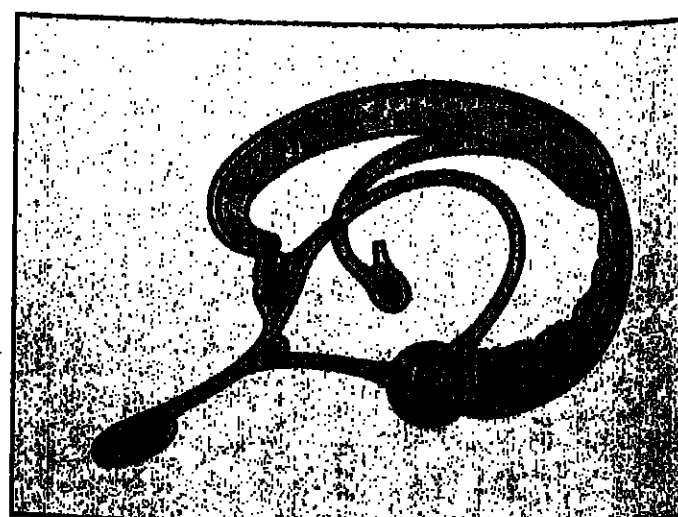
Clinical knowledge of Librium is extensive, yet its mode of action remains under continuing study. Data from animal experiments have been presented here for their intrinsic interest and because such findings often provide direction to new research, both experimental and clinical. *However, conclusions from such studies may not always be extrapolated to humans.*

### Is the limbic system the "Librium (chlordiazepoxide HCl) system"?

A great deal of experimentation on various animal species suggests that the limbic system is the principal site of action of Librium. Thus, in freely moving cats with electrodes implanted in the brain, Librium 5 mg/kg i.p. slowed electrical activity in the hippocampus, amygdala and septal areas but not in the neocortex which was significantly affected only at higher doses.<sup>1,2</sup> Current investigations on monkeys,<sup>3,4</sup> however, indicate that other subcortical structures may be implicated in the effect of Librium.

Other investigators, through electrophysiologic studies<sup>5</sup> in intact, conscious cats and monkeys, have demonstrated that chlordiazepoxide activates structures involved in the rewarding system—the preoptic area, lateral hypothalamus, septal region and hippocampal formation. At the same time, it appears to inhibit structures implicated in aversive behavior—the thalamic nuclei of the diencephalon and the midbrain reticular formation (MRF).

- References:
1. Schallek W, Kuehn A, Jew N: *Ann NY Acad Sci* 96:303-312, Jan 13, 1962
  2. Sternbach LH, Randall LO, Gustafson SR: 1,4-Benzodiazepines (Chlordiazepoxide and Related Compounds), chap. 5, in *Psychopharmacological Agents*, edited by Gordon M. New York, Academic Press, vol. 1, pp. 173-178
  3. Delgado JMR, Brucchi H, Snyder DR: *Psychosomatic Drugs and Radio-Controlled Behavior*. Film presented at the 124th annual meeting of the American Psychiatric Association, Washington DC, May 3-6, 1971
  4. Delgado JMR: Anticongressive effects of chlordiazepoxide, in *The Benzodiazepines*, edited by Gurattini S, Mussini E, Randall LO. New York, Raven Press, 1973, pp. 419-432
  5. Guerrero-Figueroa R, et al: Electrophysiological analysis of the action of four benzodiazepine derivatives on the nervous system, *ibid.*, pp. 489-511



Schema demonstrating hypothetical pathways of emotional activity and its related expression in laboratory animals.

### Clinical significance of excessive anxiety

Anxiety, when inappropriate and immoderate, may not only have adverse psychological effects but may also cause various somatic disturbances. Reduction of excessive anxiety thus contributes to relief of anxiety-linked emotional and physical disorders.

### Antianxiety action of Librium (chlordiazepoxide HCl)

The dependable action of Librium has been demonstrated in the relief of excessive anxiety and tension occurring alone or in association with functional and organic disorders—usually without adversely affecting performance. Librium is often used concomitantly, when anxiety is a contributing or complicating factor, with certain specific medications of other classes of drugs, e.g., cardiac glycosides, diuretics and antihypertensives.

Adjunctive use of Librium is recommended when counseling, reassurance or other nonpharmacologic measures alone are not considered sufficiently effective. When anxiety has been reduced to manageable levels, therapy with Librium should be discontinued.

**Librium®**  
(chlordiazepoxide HCl)  
5 mg, 10 mg, 25 mg capsules



We're still learning more about it  
to make it more useful to you.

Before prescribing, please consult complete product information, a summary of which follows:  
**Indications:** Relief of anxiety and tension occurring alone or accompanying various disease states.  
**Contraindications:** Patients with known hypersensitivity to the drug.  
**Warnings:** Caution patients about possible combined effects with alcohol and other

CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions),

following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of child-bearing age requires that its potential benefits be weighed against its possible hazards. **Precautions:** In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or overmedation,

increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Para-

doxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and

oral anticoagulants; causal relationship has not been established clinically. **Adverse Reactions:** Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin

eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making

periodic blood counts and liver function tests advisable during protracted therapy. **Supplied:** Librium® Capsules containing 5 mg, 10 mg or 25 mg chlordiazepoxide HCl. Libritabs® Tablets containing 5 mg, 10 mg or 25 mg chlordiazepoxide.



Roche Laboratories  
Division of Hoffmann-La Roche Inc.  
Nutley, New Jersey 07110

Wednesday, April 2, 1975

## Antiabortion Swing Worries Swiss, German, Italian MDs

Continued from page 1

Commenting on the case to MEDICAL TRIBUNE, a leading Swiss gynecologist noted that it took place in an area—Neuchâtel—that has hitherto been considered liberal in its interpretation of the existing legislation.

"As matters now stand, the law is applied in different ways in different cantons," Prof. William Geisendorf, of the University of Geneva, said. "Here in Geneva, for example, we take as our fundamental criterion the well-being of the mother, and so in practice we are close to the present situation in Britain and France."

Dr. Geisendorf, who recently visited the United States to study problems of family planning and abortion there, said the Neuchâtel decision seems to point to a stiffening of the conservative opposition to freer abortion, as in the United States.

The atmosphere in Italy is even more strained than in Switzerland or West Germany, following a police raid on an abortion clinic that was openly set up in Florence and provided operations by qualified medical staff at a fee of less than \$100. Those now in prison awaiting trial include the gynecologist in charge of the clinic, Dr.

Giorgio Conciari, and several of the nursing staff, and also Gianfranco Spadaccia, national leader of the Radical party, which established the clinic. As the law—an inheritance from the Mussolini regime—now stands in Italy, anyone involved in an abortion faces a prison sentence of up to five years, and there are no extenuating circumstances.

In a recent decision, the Italian constitutional court ruled that abortions are legal whenever doctors determine that pregnancy is a serious threat to the physical or psychological health of the mother, but the judges added that it is up to the Italian parliament to draw up more specific criteria.

### Court Bars Liberalization

Medical Tribune World Service

BONN, W. GERMANY—A decision by the West German Constitutional Court in Karlsruhe to reject the proposed law liberalizing abortion has been greeted with approval by the German Medical Association (Hartmannbund) here.

The law, which was accepted by a parliamentary majority last spring, was found unconstitutional by the Karlsruhe judges on the ground that it would violate the fetus's right to life.

Under the proposed law, physicians would have been permitted to carry out abortions up to the end of the 12th week of pregnancy, in line with legislation now in force in Great Britain, France, and the Scandinavian countries.

### Interim Guidelines

A new law must now be drafted by the German Government, but the court noted that in the interim period it would be permissible for a physician to carry out an abortion on one of three grounds:

- *Ethical*—e.g., if the mother was pregnant as a result of rape.
- *Genetic*—if there is a danger of fetal malformation.
- *The health of the mother*, mental or physical, if it could be endangered by the pregnancy.

A spokesman for the German Medical Association, a voluntary body that includes some 30,000 of the nation's 115,000 practitioners of medicine, said they welcomed the Court's decision because it upholds the fetus's right of protection.

"We also welcome the Court's position on permissible types of abortion because the emphasis is placed on medical rather than social considerations," the official told MEDICAL TRIBUNE.

"In our view the fetus becomes viable at nidation—or about a fortnight after conception and acquires individual rights that must be respected."

### Austrian Doctor Boycott

Medical Tribune World Service

VIENNA—More than 80 per cent of Austrian gynecologists have announced that they will boycott for professional considerations new legislation permitting abortion within the first three months of pregnancy. As a result, only 12 of the country's 83 main hospitals are accepting women seeking such intervention.

### Chin-Control Respirator



"Independence Chair" for quadriplegics susceptible to respiratory distress is equipped with portable respirator activated by chin-controlled drive unit.

## Hastings Favors Deliberation on Malpractice Bill

Continued from page 3

Now, in contrast, the congressman is hearing from almost everyone about the malpractice insurance problem. "Doctors more than anybody, of course; other professions too, but primarily the doctors," Mr. Hastings said. They're mainly concerned about "Am I covered or not?"

"Strangely enough, the person who has not expressed his concern is the person who really should, and that is the prospective patient. I don't hear from the average on-the-street constituent on this problem very often, although when you realize that malpractice insurance increases have added \$3 or \$4 a day to hospital rates you would think that the average person would be worried about the high cost of health care. I presume that most people feel they're covered by some form of insurance and so aren't really concerned about the high cost."

### Hastings Plans Bill

The medical malpractice insurance conference which Mr. Hastings and the AGPA sponsored included as participants a wide variety of persons concerned with the problem—Sen. Edward M. Kennedy (D.-Mass.) and Rep. Paul G. Rogers (D.-Fla.), chairmen of the Senate and House health subcommittees, respectively, representatives of the insurance industry and bar associations, state legislators and insurance commissioners, Department of Health, Education, and Welfare officials, academicians, and spokesmen for the American Medical and Hospital Associations.

Mr. Hastings indicated that it was likely he would introduce a bill dealing with the malpractice insurance problem since, "I don't think we have a long, long time [for detailed study of every aspect] and are going to have to do something about it."

### Tribune Economic Analysis



**Fuel Cost Jump Deepens Crisis in Real Estate**  
By Burton Farnway  
"Chilling Economy"

Thanks to the sixfold increase in the cost of fueling the country's structures, the real estate crisis is deepening. Last year, before incomes began to fall, but after fuel costs had taken their ghastly jump, a disturbing cross section of American owners of income-producing property found themselves in deep trouble. They were unable to break even on just their operating costs. Interest delinquencies ruined the REITS (Real Estate Investment Trusts) and contributed to the squeeze on the banks.

The threat of still higher fuel costs is pushing the panic button in the mortgage market. Owners of first mortgages "want out" at any salvage price. Lending institutions are anxious to avoid the complications and embarrassments that have been accompanying property ownership. They are taking their losses on "fire sales" of their mortgages—instead of foreclosing on them.

Corporate bond prices rated as "businessman's risks" follow the mortgage market. The deep discounts on mortgages are forcing sympathetic discounts on a wide range of corporate bonds with such ratings. Ironically, however, it was the headlined drop in prime interest rates that triggered the stock market's tremendous comeback. Confidence in still lower prime rates has been generating the momentum the market has developed.

But the parameters of the American economy are by no means limited to prime rate borrowers. In fact, they can expect to remain in good shape only as long as they can count on collecting from their customers. The divergence between confidence in still lower prime rates and panic about even more real estate and entrepreneurial bankruptcies suggests that the stock market may have gotten considerably ahead of itself.

I own a good many shares in a mutual fund. Most of my friends have taken a beating in their mutual funds. How do you evaluate them at this time? I am now 60 years old, have a busy practice, calculate my net worth, which is real estate, at \$500,000. Land which I purchased after World War II for \$20,000 is now bringing me \$15,000 annually and paying off a \$100,000 mortgage on it. Would it be advisable to sell off the real estate in favor of Treasury bills?

Illinois specialist

The best mutual funds are the seasoned ones which have demonstrated a capacity to grow through bad markets. If you have owned yours for some time, yours may be one of the more conservative survivors. I see no reason for you to switch out of your position, although you might, in your position, consider one-year tax empties. They may be obtained through any bank or broker.

### Ritalin® hydrochloride (methylphenidate hydrochloride) TABLETS

**INDICATION**  
Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indication as follows:  
"Possibly" effective: Mild depression  
Final classification of the less-than-effective indication requires further investigation.

**CONTRAINDICATIONS**  
Marked anxiety, tension, and agitation, since Ritalin may aggravate these symptoms. Also contraindicated in patients known to be hypersensitive to the drug and in patients with glaucoma.

**WARNINGS**  
Ritalin should not be used in children under six years, since safety and efficacy in this age group have not been established.  
Sufficient data on safety and efficacy of long-term use of Ritalin in children with minimal brain dysfunction are not yet available. Although a causal relationship has not been established, suppression of growth (i.e., weight gain and/or height) has been reported with long-term use of stimulants in children. Therefore, children requiring long-term therapy should be carefully monitored.

Ritalin should not be used for severe depression of either exogenous or endogenous origin or for the prevention of normal fatigue states.

Ritalin may lower the convulsive threshold in patients with or without prior seizures, with or without prior EEG abnormalities, even in absence of seizures. Safe concomitant use of anticonvulsants and Ritalin has not been established. If seizures occur, Ritalin should be discontinued. Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Ritalin, especially those with hypertension.

**Drug Interactions**  
Ritalin may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents and MAO inhibitors. Ritalin may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, diphenhydramine, phenytoin), phenylbutazone, and triazole. Antidepressants (imipramine, desipramine). Downward dosage adjustment of these drugs may be required when given concomitantly with Ritalin.

**Use in Pregnancy**  
Adequate animal reproduction studies to establish safe use of Ritalin during pregnancy have not been conducted. Therefore, until more information is available, Ritalin should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

**Drug Dependence**  
Ritalin should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.  
Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbance.

**PRECAUTIONS**  
Patients with an element of agitation may react adversely; discontinue therapy if necessary. Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

**ADVERSE REACTIONS**  
Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include: hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinetic; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: leukopenia and/or anemia; a few instances of scalp hair loss. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

**DOSEAGE AND ADMINISTRATION**  
**Adults**  
Administer orally in divided doses 2 or 3 times daily, preferably 30 to 45 minutes before meals. Dosage will depend upon indication and individual response.

Average dose is 20 to 30 mg daily. Some patients may require 40 to 60 mg daily. In others, 10 to 15 mg daily will be adequate. The few patients who are unable to sleep if medication is taken late in the day should take the last dose before 6 p.m.

**HOW SUPPLIED**  
Tablets, 20 mg (pink, scored); bottles of 100 and 1000.  
Tablets, 10 mg (pink, scored); bottles of 100, 500, 1000 and Accu-pak blister units of 100, 500 and 1000.  
Tablets, 5 mg (pink, scored); bottles of 100, 500 and 1000.

Consult complete product literature before prescribing.

CIBA Pharmaceutical Company  
Division of CIBA-GEIGY Corporation  
Summit, New Jersey 07901

CIBA

## What a difference a day can make

Your counsel and reassurance—and Ritalin. A logical first step in treating mild depression, and often all that's needed to bring quick symptomatic relief. Indeed, your patient may be-

gin to feel better within hours—her spirits boosted, her mood brightened. A single prescription may be all that's needed. Ritalin is usually well tolerated even by older or convalescent patients. Note, however,

that it is not indicated in the more severe depressions. But whenever depression is mild, think of Ritalin—so your patient has a better chance of waking up to a brighter tomorrow.

**Ritalin®**  
(methylphenidate)  
acts quickly to relieve symptoms in mild depression

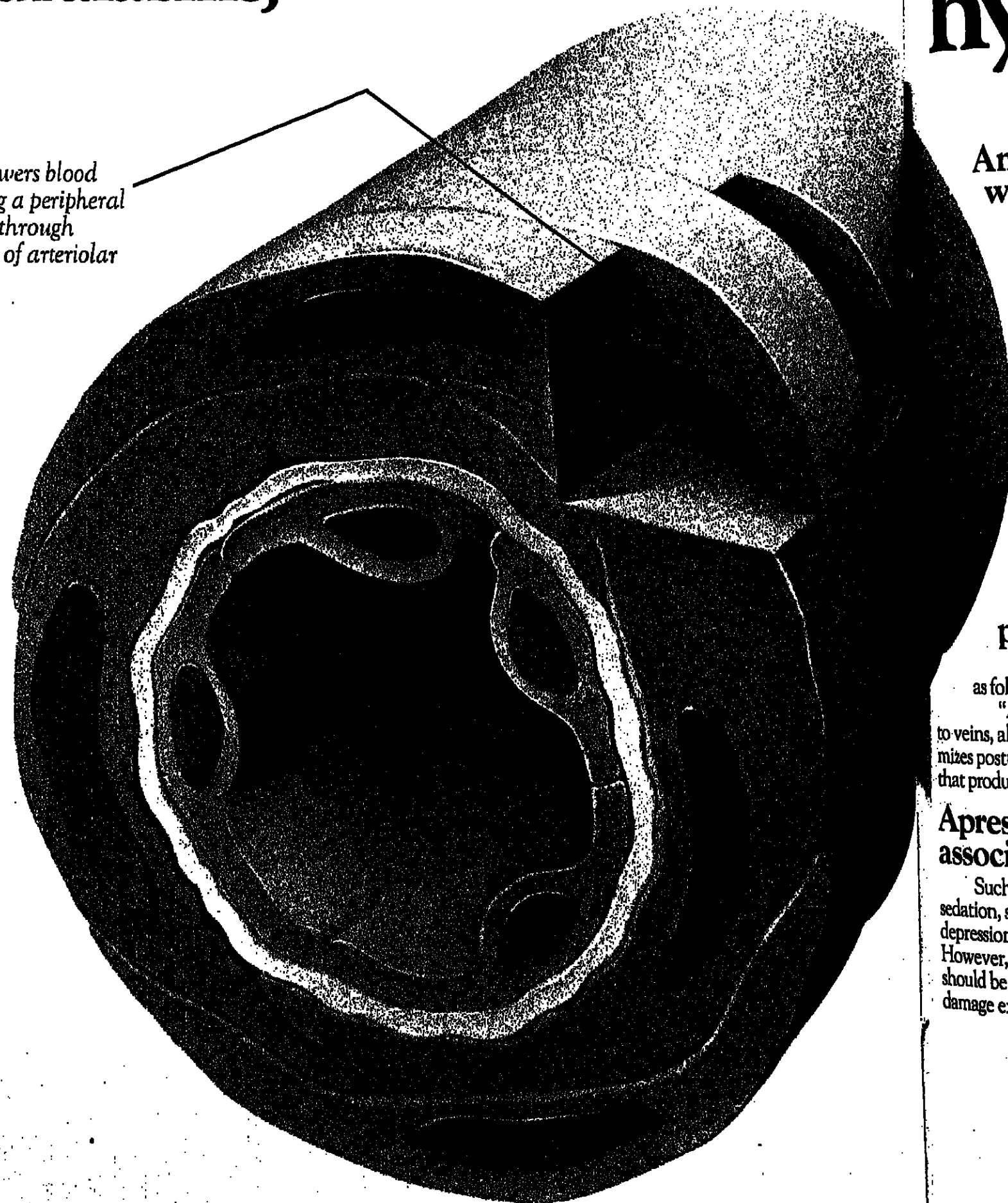
\*This drug has been evaluated as possibly effective for this indication. See brief prescribing information.



# Apresoline®...where the action is in treating hypertension

(hydralazine)

Apresoline lowers blood pressure by exerting a peripheral vasodilating effect through a direct relaxation of arteriolar smooth muscle.



## An antihypertensive idea whose time has come

Doctors who treat hypertension are increasingly interested in the one oral drug that has a mechanism of action exclusively its own — Apresoline.

Apresoline is in an antihypertensive class by itself because it reduces blood pressure through a unique mechanism. Acting at the ultimate site of hypertension, it directly relaxes arteriolar smooth muscle to decrease peripheral vascular resistance and arterial pressure. As blood pressure falls, there is an accompanying rise in cardiac output and rate.

Apresoline also maintains or increases renal and cerebral blood flow.

## Apresoline minimizes postural hypotension

Nickerson<sup>1</sup> describes the action of Apresoline as follows:

"A preferential effect on arterioles, as compared to veins, allows the increase in cardiac output and minimizes postural hypotension; the latter is much less than that produced by agents blocking sympathetic nerves."

## Apresoline avoids side effects associated with other agents

Such untoward reactions as drowsiness, lethargy, sedation, sexual dysfunction, and exacerbation of mental depression are not usually encountered with Apresoline. However, as with any antihypertensive agent, hydralazine should be used with caution where advanced renal damage exists.

## Apresoline helps tailor the regimen to the patient

When Apresoline is added to an existing antihypertensive regimen, it introduces a different and complementary pharmacologic approach to the control of your patient's hypertension.

Apresoline thus affords the physician a variety of combinations with which he can construct regimens more closely molded to individual requirements. According to Freis,<sup>2</sup> such a combination of drugs, each with a different antihypertensive mechanism, is the most effective way to control blood pressure. This may also permit lower drug dosages.

Apresoline lends itself admirably to the contemporary antihypertensive rationale and its therapeutic goals: more vigorous and more effective control of blood pressure through a plurality of mechanisms.

## Apresoline: used effectively in the VA studies

Apresoline was one of the three basic drugs used in two published VA cooperative studies.<sup>3,4</sup>

References: 1. Nickerson M. Antihypertensive agents and the drug therapy of hypertension. In Goodman LS, Gilman A (eds): *The Pharmacological Basis of Therapeutics*, ed 4. New York, The Macmillan Company, 1970, p 729. 2. Freis ED: Hypertension: a controllable disease. *Clin Pharmacol Ther* 13:627-632, 1972. 3. Effects of treatment on morbidity in hypertension: Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. Veterans Administration Cooperative Study Group on Antihypertensive Agents. *JAMA* 202:1028-1034, 1967. 4. Effects of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. Veterans Administration Cooperative Study Group on Antihypertensive Agents. *JAMA* 213:1143-1152, 1970.

Next page: Apresoline (hydralazine) and the Hypertension Task Force

### Apresoline® hydrochloride (hydralazine hydrochloride)

**INDICATIONS**  
Essential hypertension, alone or as an adjunct.  
**CONTRAINDICATIONS**  
Hypersensitivity; coronary artery disease; mitral valvular rheumatic heart disease.  
**WARNINGS**  
Chronic administration of doses over 400 mg per day may produce an arthritis-like syndrome.

ing to a clinical picture simulating acute systemic lupus erythematosus. This may also occur at lower doses. Most of these reactions are reversible upon withdrawal of therapy, but long-term treatment with steroids may be necessary and residue have been detected many years later. Complete blood counts, L.E. cell preparations and antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy, even though patient is asymptomatic. These studies are also indicated in the presence of any unexplained symptoms.  
Use MAO inhibitors with caution.

**Use in Pregnancy**  
The drug should be used only when, in the judgment of the physician, it is deemed essential to the welfare of the patient.  
**PRECAUTIONS**  
Use cautiously in suspected coronary artery or other cardiovascular diseases, cerebral vascular accidents, and advanced renal damage. Postural hypotension may occur, and the pressor response to epinephrine may be reduced.  
Peripheral neuritis, evidenced by paresthesias, numbness, and tingling, has been observed. Rubbed evidence suggests an antipyridoxine effect

and addition of pyridoxine to the regimen if symptoms develop.  
Blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura, have been reported rarely. If such abnormalities develop, discontinue therapy. Periodic blood counts are advised during prolonged therapy.  
**ADVERSE REACTIONS**  
Common: Headache; palpitations; anorexia; nausea; vomiting; diarrhea; tachycardia; angina pectoris; less frequent: Nasal congestion; fluid retention; conjunctivitis; peripheral neuritis.

evidenced by paresthesias, numbness, and tingling; edema; dizziness; tremors; muscle cramps; psychotic reactions characterized by depression, disorientation, or anxiety; hypersensitivity (including rash, urticaria, pruritus, fever, chills, arthralgia, myalgia, and, rarely, vasculitis); constipation; difficulty in micturition; dyspnea; paralytic ileus; lymphadenopathy; splenomegaly; blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura; hypotension; paradoxical pressor response.

**DOSEAGE**  
Initiate therapy in gradually increasing dosages, adjust according to individual response. Start with 10 mg 4 times daily for the first 2 to 4 days, increase to 25 mg 4 times daily for balance of first week. For second and subsequent weeks, increase dosage to 50 mg 4 times daily. For maintenance, adjust dosage to lowest effective level.  
The frequency of toxic reactions, particularly the L.E. cell syndrome, is high in the group of patients receiving large doses of Apresoline.  
In a few resistant patients, up to 300 mg Apresoline daily may be required for a significant antihyper-

tensive effect. In such cases, a lower dosage of Apresoline combined with a thiazide, reserpine, or other antihypertensive agent may be considered. However, when combination therapy, individual titration is essential to insure the lowest possible therapeutic dose of each drug.  
**HOW SUPPLIED**  
Tablets, 10 mg (pale yellow, dry-coated); bottles of 100 and 1000.  
Tablets, 25 mg (dark blue, dry-coated); bottles of 100, 500, and 1000.  
Tablets, 50 mg (dark, dry-coated); bottles of 100, 500, and 1000.

Tablets, 100 mg (peach, dry-coated); bottles of 100.  
Consult complete literature before prescribing.  
CIBA Pharmaceutical Company  
Division of CIBA-GEIGY Corporation  
Summit, New Jersey 07901

C I B A

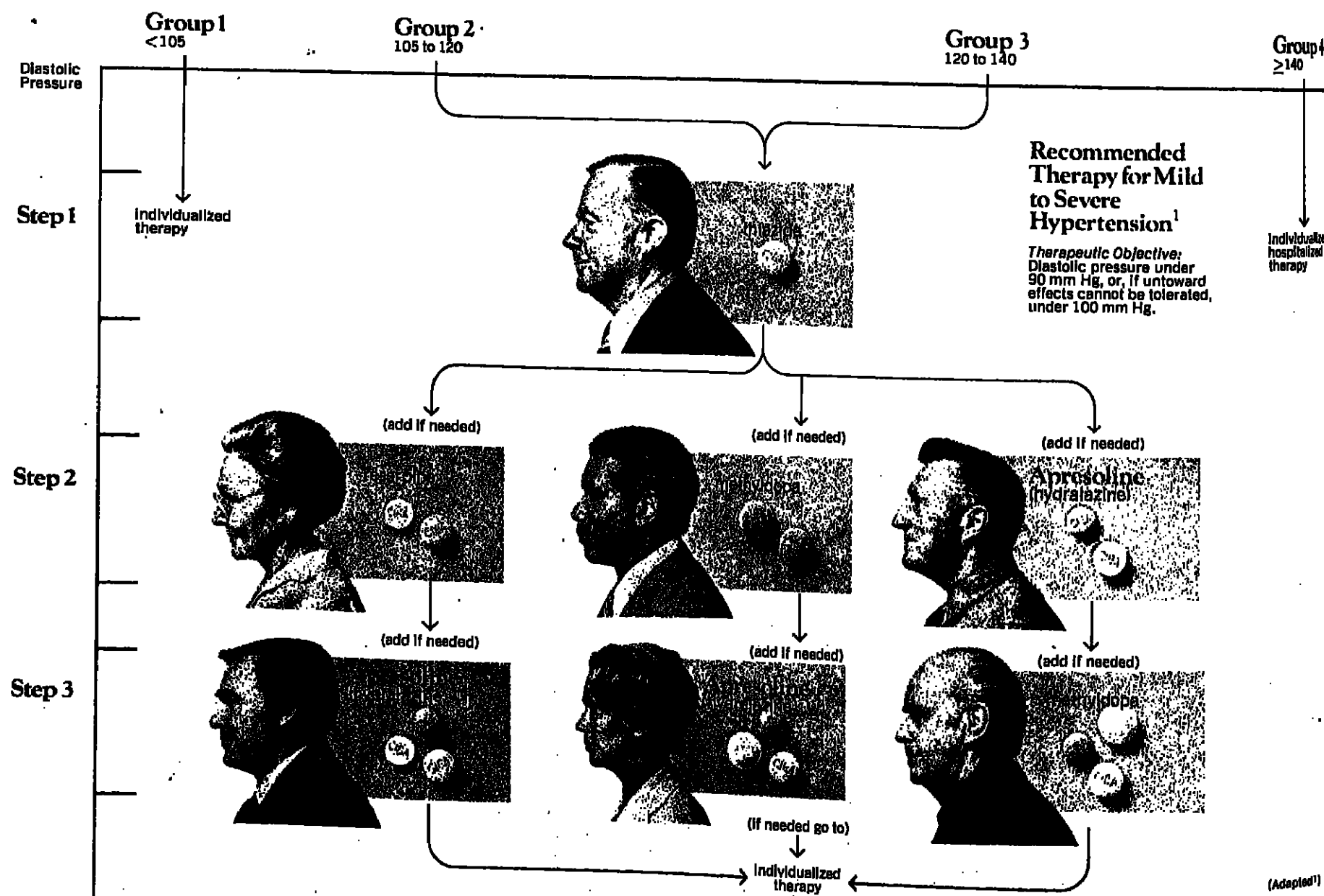
# Apresoline... (hydralazine) part of the Hypertension Task Force "plan of action"

In September 1973, Task Force I of the National High Blood Pressure Education Program recommended a series of antihypertensive regimens for groups with hypertension ranging from mild to severe. Hydralazine—used in combination with sympathetic-inhibiting and/or diuretic antihypertensive

agents—was a specific recommendation for "second step" and "third step" therapy in patients with diastolic pressures ranging from 105 to 140 mm Hg. Hydralazine played a prominent role in the Task Force regimens because of its compatibility with almost any antihypertensive regimen. For

Apresoline can be combined advantageously with nearly all diuretics and sympathetic inhibitors.

Reference: 1. Report of Task Force I, National High Blood Pressure Education Program: Recommendations for a National High Blood Pressure Program Data Base for Effective Antihypertensive Therapy, Sept. 1, 1973, DHEW Publication No. (NIH) 74-593.



**Apresoline<sup>®</sup> (hydralazine)**  
...acts directly at the ultimate  
site of hypertension  
...brings something  
special to almost any  
antihypertensive  
regimen

For brief prescribing information,  
please see preceding pages.



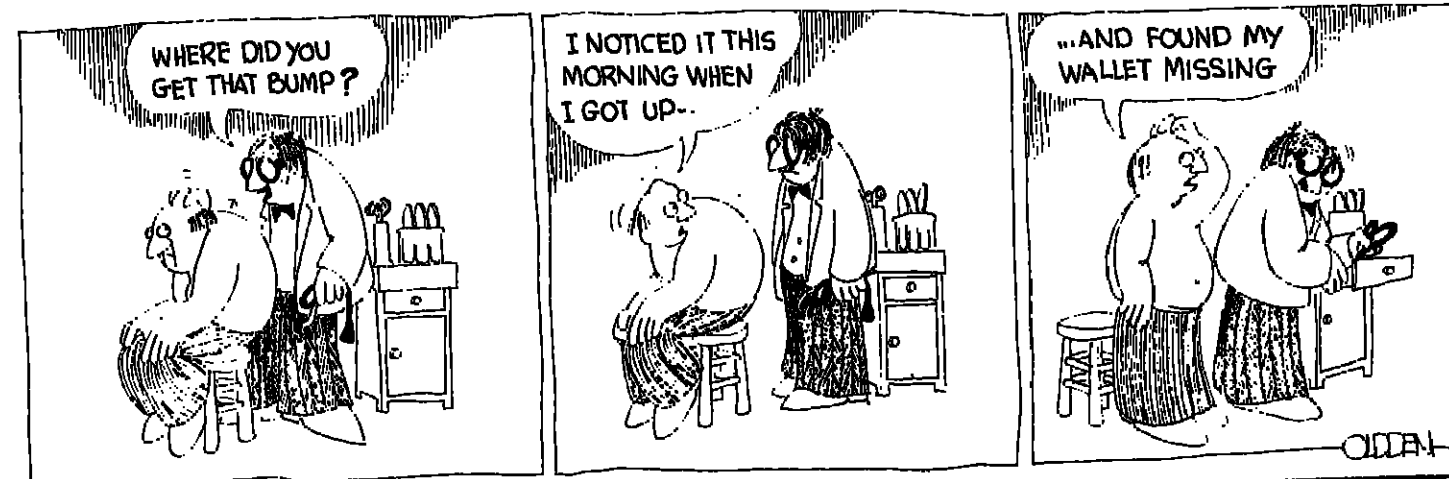
C I B A

Wednesday, April 2, 1975

MEDICAL TRIBUNE

by Olden

## Clinical Trials



## TRIBUNE SPORTS REPORT

### Data Lacking on What Effect 'The Pill' Has on Performance

Medical Tribune Report

CLEVELAND—Although many female athletes today are on oral contraceptives, there are no data on whether the medication benefits or hinders athletic performance or whether it may even present a health hazard in such patients, according to Dr. Lester Ballard, head of gynecology at the Cleveland Clinic.

"We need to find this out," he told a sports symposium there. "For the moment, however, all we can do is individualize and test each patient, to see if she is better on or off the pill."

"Theoretically, a high-progestin pill could help athletic performance, but it's difficult to make a definitive statement about this potential because there hasn't been any study."

Such a pill, he noted, can also help the girl athlete with "heavy periods, breast tenderness, and bloating" due to hyperestrinism.

#### Slight Risk Seen

As to whether the use of oral contraceptives might make the female athlete more susceptible to a cerebrovascular accident or phlebitis, Dr. Ballard said:

"I think there may be a slight risk, but again there's no good hard data on this. I do know that when we do gynecological elective surgery today because there is increased clotting, it's a good idea to have the girls off the pill for two or three months."

Dr. Ballard was one of several speakers, including a woman coach, who addressed themselves to questions of female physiology and its relationship to participation in sports.

"Today, with all the dieting that's going on, many girls need supplemental iron," Dr. McLaughlin said. "Taking the blood counts of the girls on our teams—they were a bit low, and just on that basis I'd recommend iron for about 75 per cent of them... not because they're athletes, but just for their general health."

Does menstruation itself have any effect on sports performance? According to Dr. Ballard, it does for the girl who suffers cramps, headache, and fluid retention, and whose symptoms a birth-control pill does not help to alle-

viate. Some girls, however, feel better able to compete during their menstrual periods, he noted.

"The perineal pads should be thrown away" by athletes and by other girls as well, he said. For those with heavy periods, he recommended the use of two tampons instead of one.

With regard to swimming during menstruation, he commented:

"There's no problem because the vagina does exclude water. Also, the blood from the endometrium is sterile, and the only thing the blood picks up along the way is the normal vaginal flora, which is similar to what is found in the nasopharynx. So there's no problem if the blood does escape into the water of the pool."

Judy Devine, field hockey and basketball coach at Kent State University, Kent, Ohio, said that special breast protectors, such as plastic brassieres,

do not seem warranted, even in the sports she coaches, with a fairly high degree of body contact.

"I have not found any incidence of breast contusion that amounts to anything at all," she reported.

She added that she has no rule on whether a girl may compete bra-less.

"I do have a couple of girls who compete bra-less, but one always wears a swimsuit under her uniform. It is uncomfortable to run without some kind of support, and I think they know this, so they either wear a bra or they buy a tight blouse."

#### 'Thermostat' Set Higher

Dr. Thomas McLaughlin, team physician for women's sports at Case Western Reserve University, said that besides the obvious differences in size, strength, and body fat between males and females, there is also the temperature-regulation mechanism to consider. Since the hypothalamic "thermostat" is set higher in females, they would be at higher risk of heat stroke and heat exhaustion in any kind of mid-August practice in heavy protective clothing, such as male football players endure, he said.



## IMMATERIA MEDICA

### Zero Mostel's Baggy Union Suit

We compulsively clip anything that amuses, outrages, fascinates, or reminds us of something. A hopeless case, we'll admit; the missing Collyer brother, my good wife says. And the sequelae are dreadful. You have to sit down and go through all these fantastic clips and throw them all out to make room for more.

We try to stay just about a year behind our blade. Thus it happened recently that we were again chortling happily over pictures of Zero Mostel running around in his union suit—long baggy underwear, to the denim generation—in the *New York Times* of Feb. 10, 1974. It's been a long time since we saw a union suit so well modelled. It reminded us of our father's, but it also reminded us of a story Zero once told.

He had been, he confided, going to see a psychiatrist about his inner man and had been having a terrible time. It seemed that the psychiatrist considered him and his inner man very, very funny. He laughed uproariously at every story Zero told of his life in the spotlight, his pretzel childhood, his adolescent struggles to become Babe Ruth and Rudolph Valentino, his poverty-ridden cold water flat and his efforts to be an abstract artist on the W.P.A.

Zero had the psychiatrist in the aisles, he told us with delight. "And I am also paying him; which is a real tale of woe. When is treatment going to begin? Am I always going to be onstage?" he howled.

The psychiatrist had his office couch within one of his apartment's large rooms. One day as Zero was detailing his hilarious misery, the psychiatrist was laughing so hard that tears were running down his cheeks. As Zero's story began to mount, the psychiatrist cried out, "Stop! Stop!"

Ah, thought Zero, treatment is at last to begin. He quieted instantly.

The psychiatrist, wiping away his tears, bounded for the door. "Do you mind if I bring in my wife?"

It was a wonderful treatment, Zero said. It cured him and his inner man. What a psychiatrist!